Original Research Article

DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20200691

Incidence of reactive thrombocytosis in serious bacterial infections in children aged two months to twelve years and its usefulness as a predictor of serious bacterial infections

Thahseen Nilofar Sahubar Sadique*, Thrilok Natarajan, Kabilan Shanmugham, Suresh Kumar Veluchamy

Department of Paediatrics, Institute of Child Health and Hospital for Children, Madras Medical College, Egmore, Chennai, Tamil Nadu, India

Received: 29 November 2019 Revised: 08 January 2020 Accepted: 27 January 2020

*Correspondence:

Dr. Thahseen Nilofar Sahubar Sadique, E-mail: milmikach@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: The aims of the study were to estimate the incidence of reactive thrombocytosis(RT) among febrile children aged 2 months to 12 years and to identify any differences in age group and gender in mounting thrombocytosis as a response to infection, to identify if thrombocytosis occurred preferentially in any particular group of serious bacterial infections(SBI), to compare thrombocytosis with other parameters like total white cell count, C-reactive protein(CRP), cultures etc. and to assess the utility of platelet count as a potential predictor of serious bacterial infection.

Methods: This was a prospective study done in Institute of Child Health and Hospital for children, Madras Medical College from September 2015 to July 2016. Inclusion criteria: Children aged 2 months to 12 years with symptoms of fever less than 6 days admitted in the paediatric wards and those seen at the outpatient department. Exclusion criteria: Children having received parenteral antibiotics.

Results: Of the 500 children, 142 (28.4%) had reactive thrombocytosis. RT was mild in 120 children (24%), moderate in 16 children (3.2%), severe in 4(0.8%) and extreme in two children (0.4%). This study showed that 36.48% (85 / 233) of children under 1 year had RT (p = 0.0002). There was no significant sex related difference in mounting RT. Out of 500 children included in the study, serious bacterial infection was diagnosed among 171 children (34.2%). Pneumonia (n=100) was the most common SBI followed by urinary tract infections (n=33), meningitis (n=23), sepsis (n=15). This study showed that RT has a moderate ability to predict serious bacterial infections (AUC=0.78; PPV-75.35%).

Conclusions: Incidence of reactive thrombocytosis in febrile children aged 2 months to 12 years is 28.4%. It occurs more frequently in infants and without any sex predilection. RT is associated with leucocytosis, positive CRP, positive Chest X ray findings, positive urine culture and positive CSF findings. This shows that RT has a moderate ability in predicting SBI in children.

Keywords: Empyema, Platelet count, Pneumonia, Predictor, Reactive thrombocytosis, Serious bacterial infection

INTRODUCTION

Platelets can behave like acute phase reactants. Thrombocyte synthesis is ignited by interleukin-6 which enhances megakaryopoiesis directly and indirectly by inducing Thrombopoietin (TPO) production in the liver.^{1,2} Variations in platelet count provide important clues to disease processes. Bacterial infections can cause aberration in platelet counts. While thrombocytopenia is more frequently associated with an increase in mortality, the impact of thrombocytosis remains under reported.

Thrombocytosis is defined as platelet count above 5 lakhs /mm³. Thrombocytosis in childhood rarely causes complications, although it is frequently concerning. The causes of thrombocytosis may be Primary (as in Polycythaemia Vera, Essential thrombocythemia) or Reactive.³ Reactive thrombocytosis is also known as secondary thrombocytosis. It is impermanent and subsides when the primary stimulus comes to an end. Reactive thrombocytosis is caused by an add on release of cytokines as a response to infections, inflammation, tissue trauma, etc.⁴ One single common bacterial infection most often associated with RT is pneumonia.5 In a patient with RT, pharmacologic therapy is not needed as thrombo-haemorrhagic consequences are extremely rare. Studies have not shown any advantage of prophylactic administration of antithrombotic or antiplatelet agents.⁶ Hence, use of these drugs is not generally warranted. The primary treatment of RT should address the underlying cause. The overall prognosis in patients with RT reflects that of the underlying associated condition.

The aims of the study were to estimate the incidence of reactive thrombocytosis (RT) among febrile children aged 2 months to 12 years and to identify any differences in age group and gender in mounting thrombocytosis as a response to infection, to identify if thrombocytosis occurred preferentially in any particular group of serious bacterial infections (SBI), to compare thrombocytosis with other parameters like total white cell count, C-reactive protein (CRP), cultures etc. and to assess the utility of platelet count as a potential predictor of serious bacterial infection.

METHODS

This prospective study was conducted at Institute of Child Health and Hospital for children, Madras Medical College from September 2015 to July 2016. The protocol was approved by Institutional Ethics Committee. Children who met the inclusion criteria were recruited into the study after obtaining informed written consent from parents.

Children aged 2 months to 12 years with symptoms of fever less than 6 days admitted in the paediatric wards and those seen at the Outpatient Department were included in the study. Children having received parenteral antibiotics were excluded from study.

Detailed history taking, and clinical examination was done. Important clinical findings were documented.Blood was taken from a peripheral vein by venepuncture and was sent for the various investigations mentioned.Urine was collected by midstream clean catch technique. Investigations like complete blood count(CBC), C- reactive protein(CRP), peripheral smear, blood culture, urine analysis, urine culture, chest X-ray were performed. Cerebrospinal fluid (CSF) analysis was done when indicated. CBC was analyzed using automated cell counter (Sysmex KX-21N[™] Automated Haematology Analyser).

The platelet counts were collected, and severity of thrombocytosis was graded according to study definition. Children with thrombocytosis who meet the clinical diagnostic criteria for diagnoses other than SBI such as Iron Deficiency anemia, connective tissue disorders were excluded from the study. The findings suggestive of SBI in chest x-ray included pneumonitis, bronchopneumonia, lobar consolidation, and empyema. All the data were entered in the Microsoft Excel spread sheet and analysed using SPSS Software version 20.0. The primary outcome was expressed as proportion. Chi square test was used to determine the association between outcome variable and dependent variable. P value less than 0.05 was considered significant. Reactive thrombocytosis was compared to different parameters using univariate analysis.

Serious bacterial infections considered in this study were pneumonia, urinary tract infection (UTI), meningitis, sepsis-culture positive and sepsis-culture negative.

Table 1: Classification of thrombocytosis.

Mild	Platelet count 5-7 lakhs per cu.mm of blood
Moderate	Platelet count 7-9 lakhs per cu.mm of blood
Severe	Platelet count 9-10 lakhs per cu.mm of blood
Extreme	Platelet count > 10 lakhs per cu.mm of blood

The study definitions which were used are given below:

Pneumonia Severe or very severe (as per IMNCI clinical guidelines) and/or radiological features suggestive of pneumonia.

Meningitis CSF findings suggestive of bacterial infection such as pleocytosis, protein elevation, gram stain or positive growth on culture.

Urinary tract infection Growth in urine culture

Sepsis Culture positive and probable/culturenegative/clinical sepsis (clinical signs and symptoms of sepsis without growth of any pathogen on culture)

Fever Axillary temperature $\geq 38^{\circ}C$ (100.4°F)

Thrombocytosis Platelet count \geq 51akh per cu.mm of blood.

Leucocytosis WBC count $\geq 11,000$ cells per cu.mm of blood

Pyuria Presence of 10 or more white cells per cubic millimetre in a centrifuged urine specimen

Sepsis Life-threatening organ dysfunction caused by a dysregulated host response to infection.

RESULTS

Of the 500 children, 142 (28.4%) had reactive thrombocytosis. Mean platelet count of the study

population was 3.93 lakhs per cu.mm of blood. The highest platelet count observed in this study was 10.18 lakhs per cu.mm of blood.

Twenty children had platelet counts less than one lakh. From this study, the incidence of RT was calculated to be 28.4% (95% Confidence Interval= 24.45% to 32.35%). RT was mild in 120 children (24%), moderate in 16 children (3.2%), severe in four (0.8%) and extreme in two children (0.4%) as seen in Table 2.

Table 2: Comparison of reactive thrombocytosis with different study parameters.

Study parameter	Reactive thrombocytosis present	Reactive thrombocytosis absent	p value		
Age					
Less than 1 year	85	148	0.0002		
1 to 5 years	47	148	0.0002		
Above 5 years	10	62			
Sex					
Male	88	205	0.3655		
Female	54	153	-		
Total WBC count					
Normal	32	208	0.0001		
Increased	110	150			
Neutrophil percent					
Normal	118	276	0.15		
Increased	24	82	-		
Toxic granules / neutrop	hilia on peripheral blood smear		_		
Absent	340	136	0.820		
Present	18	6	-		
Pyuria					
present	0	8	0.1126		
absent	142	350	-		
Pneumonia on CXR					
Present	56	44	0.0001		
Absent	86	314	-		
C-reactive protein					
Positive	89	86	0.0001		
Negative	53	272	-		
Blood culture					
Growth absent	138	352	0.4		
Growth present	4	6	•		
Urine culture					
Growth absent	125	342	0.0044		
Growth present	17	16			
CSF findings suggestive of meningitis					
Absent	0	20	0.0001		
Present	23	0			

A total of 500 children were studied including 293 boys (58.6%) and 207 girls (41.4%). Table 2 shows that among them 46.6% (233 out of 500) belonged to less than 1 year of age (2 months to 12 months), 39% (195 out of 500) belonged to 1 to 5 years of age and 14.4% (72 children out of 500) belonged to 6 to 12 years of age. Mean age of

the study population was 32.4 months. This study showed that 36.48% (85 / 233) of children under 1 year had RT which was considered statistically significant (p = 0.0002) when compared to children between 1 to 5 years of age of whom 24.1% (47/195) had RT and children beyond 5 years of whom 13.89% (10/72) had RT, as

depicted in Table 2. There was no significant sex related difference in distribution of RT (p=0.3655).

Out of 500 children included in the study, SBI was diagnosed among 171 children (34.2%).Pneumonia (100 out of 171) was the most common SBI followed by urinary tract infection (n=33), meningitis (n=23), sepsis (n=15)of which culture negative clinical sepsis was 5. From table 2 it is seen that of the 142 children with RT 107 had one of the SBI. Pneumonia was diagnosed in 56 out of 107(52.34%), UTI in 17 of 107(15.89%), meningitis in 23(21.5%), culture positive sepsis in 6(5.61%) and culture negative sepsis in 5 of the children (4.67%). Out of 142 children with reactive thrombocytosis, 35 children did not have any SBI. Among the 500 children with fever, 48% of children had WBC count within the normal range while 52% (260 out of 500) showed leucocytosis. Only 21.2% (106 out of 500) showed neutrophil percentage above normal range. Peripheral smear with toxic granules and/or neutrophilia was observed in only 24 children (4.8%). Pyuria was observed only in 8 of the 500 children (1.6%). Hundred children showed radiological features of pneumonia (29.2%). A positive CRP was observed in 175 out of 500 children with fever (35%). Only 10 children had a positive blood culture (2%) and 33 children showed positive urine culture (6.6%). CSF analysis was done on 47 children as indicated. 23 out of 47 showed CSF findings suggestive of meningitis as evidenced by any one of cellular pleocytosis (cytology), raised protein levels above normal (biochemistry) or a positive gram stain or culture (microbiology). All the above details are summated in Table 2.

DISCUSSION

The study sample was representative of children with fever visiting or admitted in a tertiary care centre in south India. In this study 28.4% children had reactive thrombocytosis. The frequency of RT in this study was comparable with the results of previous studies by Fouzas et al and Manzoor S et al.^{8,9}

However, majority of the cases had only mild RT. It was noticed that clinical parameters like heart rate, temperature, respiratory rate did not have a statistically significant association with reactive thrombocytosis which is beyond the scope of objectives of this study. RT was seen more in children with pneumonia than in other serious bacterial infections considered in the study. Two children had empyema in this study and both of them showed extreme range of RT (platelet >10 lakhs).¹⁰ This again shows that RT is a very common phenomenon accompanying lower respiratory tract infections. RT showed a very statistically significant relationship to leucocytosis. But it did not show a statistically significant relationship to neutrophil percentage, peripheral smear findings or pyuria. Chest x-ray findings and qualitative CRP both showed statistically significant relationship with RT. Blood culture did not exhibit a statistically

significant relationship to RT. This could possibly be attributed to the overall low bacteriological yield on blood culture in the centre. When there was a positive blood culture, the child did show severe or extreme thrombocytosis. Most common pathogen isolated in blood culture was Staphylococcus aureus and it is alarming to note that methicillin resistant strains are on the rise. A positive urine culture and positive CSF findings were statistically significant with respect to RT.¹¹

Thus, Reactive thrombocytosis is present in febrile children when there is an associated leucocytosis, positive CRP, a growth in urine culture or when the CSF findings are suggestive of bacterial meningitis. From likelihood ratios, AUC and the statistical analysis it is evident that RT has a moderate ability to predict serious bacterial infections (Fouzas et al AUC=0.74 vs. Manzoor S et al AUC=0.76 vs. this study AUC=0.78 based on the parameters in Table 3) which is in concordance to the previous studies.

Table 3: Assessment of utility of reactivethrombocytosis as a predictor of seriousbacterial infections.

Parameters	Value	95% confidence interval
Sensitivity	62.57%	54.86% to 69.84%
Specificity	89.36%	85.52% to 92.48%
Positive predictive value	75.35%	67.42% to 82.19%
Negative predictive value	82.12%	77.75% to 85.95%
Likelihood ratio +	5.88	4.21 to 8.210
Likelihood ratio -	0.42	0.34 to 0.51
Disease Prevalence	34.20%	30.05% to 38.54%
Pre-test probability	0.34	
Post-test probability	0.75	

CONCLUSION

Incidence of reactive thrombocytosis in febrile children aged 2 months to 12 years is 28.4%. It occurs more frequently in infants and without any sex predilection. RT is associated with leucocytosis, positive CRP, positive Chest X ray findings, positive urine culture and positive CSF findings. This shows that RT has a moderate ability in predicting SBI in children.

ACKNOWLEDGEMENT

Author would like to thank Dr. Somasekar Ramaswamy, Professor of Paediatrics, Institute of Child Health and Hospital for Children, Madras Medical College, Egmore, Chennai, Tamilnadu, India.

Funding: No funding sources Conflict of interest: None declared *Ethical approval: The study was approved by the Institutional Ethics Committee*

REFERENCES

- 1. Osovsky M, Tamary H, Merlob P. Neonatal thrombocytosis following G-CSF treatment. Clin Toxicol. 2007 Jan 1;45(7):801-2.
- 2. Yip J, Shen Y, Berndt MC, Andrews RK. Primary platelet adhesion receptors. IUBMB life. 2005 Mar 1;57(2):103-8.
- Kliegman RM, Behrman RE, Jenson HB, Stanton BM. Nelson textbook of pediatrics. Elsevier Health Sciences; 2007 Aug 15.
- 4. Hollen CW, Henthorn J, Koziol JA, Burstein SA. Elevated serum interleukin-6 levels in patients with reactive thrombocytosis. British J Haematol. 1991 Oct;79(2):286-90.
- 5. Vlacha, V, Feketea G. Thrombocytosis in pediatric patients is associated with severe lower respiratory tract inflammation. Archiv Med Resea. 2006;37(6):755-9.
- 6. Denton A, Davis P. Extreme thrombocytosis in admissions to paediatric intensive care: no requirement for treatment. Archives of disease in childhood. 2007 Jun 1; 92(6):515-6.
- 7. Dame C, Sutor AH. Primary and secondary thrombocytosis in childhood. Br J Haematol. 2005;129(2):165-77.

- Fouzas S, Mantagou L, Skylogianni E, Varvarigou A. Reactive thrombocytosis in febrile young infants with serious bacterial infection. Indian Pediatr. 2010 Nov 1;47(11):937-43.
- Manzoor S, Wani K, Alaqaband MM, Chib R, Malik I. Thrombocytosis as Potential Diagnostic Tool for Serious Bacterial Infection In Febrile Infants; Srinagar, India. Interna J Pediatr. 2014;2(4);413-20.
- Wolach B, Morag H, Drucker M, Sadan N. Thrombocytosis after pneumonia with empyema and other bacterial infections in children. Pediatr Infect Disea J. 1990 Oct 1;9(10):718-21.
- 11. Garoufi A, Voutsioti K, Tsapra H, Karpathios T, Zeis PM. Reactive thrombocytosis in children with upper urinary tract infections. Acta Paediatrica. 2001 Apr 1;90(4):448-9.

Cite this article as: Sadique TNS, Natarajan T, Shanmugham K, Veluchamy SK. Incidence of reactive thrombocytosis in serious bacterial infections in children aged two months to twelve years and its usefulness as a predictor of serious bacterial infections. Int J Contemp Pediatr 2020;7:626-30.