Respiratory Syncytial Virus-Positive Bronchiolitis in Hospitalized Infants is Associated with Thrombocytosis

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ABSTRACT: **Background:** Secondary thrombocytosis is associated with a variety of clinical conditions, one of which is lower respiratory tract infection. However, reports on thrombocytosis induced by viral infections are scarce.

Objectives: To assess the rate of thrombocytosis (platelet count › 500 x 10^9/L) in hospitalized infants with bronchiolitis and to investigate its potential role as an early marker of respiratory syncytial virus infection.

Methods: Clinical data on 469 infants aged ≤ 4 months who were hospitalized for bronchiolitis were collected prospectively and compared between RSV-positive and RSV-negative infants.

Results: The rate of thrombocytosis was significantly higher in RSV-positive than RSV-negative infants (41.3% vs. 29.2%, $P = 0.031$). The odds ratio of an infant with bronchiolitis and thrombocytosis to have a positive RSV infection compared to an infant with bronchiolitis and a normal platelet count was 1.7 ($P = 0.023$, 95% confidence interval 1.07–2.72). There was no significant difference in mean platelet count between the two groups.

Conclusions: RSV-positive bronchiolitis in hospitalized young infants is associated with thrombocytosis.

IMAJ 2010; 12: 39–41

KEY WORDS: bronchiolitis, thrombocytosis, respiratory syncytial virus

Thrombocytosis in children is usually a result of a reactive process. The estimated incidence of reactive thrombocytosis in hospitalized children is 6%–15%, with the highest rates in the under-24 month age group [1]. Pediatric reactive thrombocytosis is most often secondary to an acute or chronic infection (37–78%) [1], especially of the respiratory tract (60–80%) [1]. Although the specific agents have not been fully identified, bacterial infections such as pneumonia and empyema are thought to account for most cases [1-4]. Reports on thrombocytosis induced by viral infections are scarce.

RSV = respiratory syncytial virus

The aim of the present study was to study the platelet count and the rate of thrombocytosis in hospitalized infants with RSV-positive and RSV-negative bronchiolitis.

PATIENTS AND METHODS

A prospective design was used. The study group comprised all infants aged 4 months or less hospitalized for bronchiolitis in the three pediatric departments of our tertiary childrens hospital (Department of Pediatrics C from 1 December 2005 to 28 February 2006; Departments of Pediatrics A, B and C from 1 December 2006 to 15 March 2007 and from 1 December 2007 to 29 February 2008).

The diagnosis of bronchiolitis was based on findings of acute wheezing or chest retractions in association with an upper respiratory tract infection (either by history or as indicated on physical examination by cough or rhinorrhea). Infants with a bacterial co-infection (meningitis, bacteremia, pyelonephritis or pneumonia), a chronic disease (heart failure, lung disease), or gestational age below 32 weeks were excluded.

All patients received routine care by the medical staff. Maximal temperature was defined as the highest rectal temperature recorded in the emergency department or at the time of admission to the department. Arterial oxygen saturation was measured by toe or finger pulse oximetry with the patient breathing room air. A bronchiolitis score modified from Wang et al. [5] was assessed at admission, prior to respiratory treatment (except oxygen) using the scale shown in Table 1. Nasopharyngeal aspirates were obtained on admission and sent for rapid RSV antigen detection by enzyme-linked immunoassay. Thrombocytosis was defined as a platelet count of more than 500 x 10^9/L. Levels of > 500 x 10^9/L to ≤ 700 x 10^9/L were considered mild thrombocytosis, levels of > 700 x 10^9/L to ≤ 900 x 10^9/L as moderate thrombocytosis, and levels of > 900 x 10^9/L as severe thrombocytosis [1]. For the purpose of the study only the first platelet count taken upon admission was used.

The following data were obtained: patient age and gender, birth weight and gestational age, duration of illness before admission, bronchiolitis score, and laboratory results at the

Table 1. Calculation of bronchiolitis score

	Bronchiolitis score		
Sign/Symptom	0	1	2
Respiratory rate	‹ 40	≥ 40 and ≤ 60	› 60
Work of breathing	None to mild inter - costal retractions or nasal flair	Moderate intercostal and suprasternal retractions, grunting, flair	Severe intracostal retraction, nasal flair, subcostal retractions
Breath sounds	Minimal wheeze/rales with bilateral air entry	Diffuse wheeze/rales with decreased air entry, increased expiratory phase	Diminished breath sounds with severely impaired air entry
O_2 saturation	› 92%	≤ 92 and ≥ 90%	‹ 90%
Eating habits	Regular	Less than usual	Inability to eat

Table 2. Comparison of clinical and laboratory data between RSV-positive and RSV-negative infants with bronchiolitis

		RSV-positive (n=363)	RSV-negative (n=106)	*P* value
Age (wks) ± SD	Mean	7.6 ± 4	7 ± 3.9	0.2457
	Range	1–17	1.5–19	
Days of illness before admission (days) ±SD	Mean	3.6 ± 2.2	4 ± 2.5	0.0923
	Range	1–14	1–14	
Maximal temperature (0C) ± SD	Mean	37.9 ± 0.7	37.9 ± 0.8	0.6406
	Range	35–39.8	36.4–40.4	
Bronchiolitis score ± SD	Mean	2.7 ± 1.7	2.4 ± 1.7	0.0628
	Range	0-8	0-8	
Hemoglobin (g/dl) ± SD	Mean	11.5 ± 1.9	11.5 ± 1.9	0.8197
	Range	7.7–19.4	7.8–19.4	
Hematocrit (%) ± SD	Mean	33.4 ± 6.2	33.2 ± 5.6	0.8288
	Range	22.7–68.4	22.4–-54.9	
Platelet count (K/µl) ± SD	Mean	470.2 ± 137.8	460.6 ± 145.5	0.5374
	Range	75–844	130–918	
% thrombocytosis		41.3%	29.2%	0.031

time of admission, including hemoglobin, hematocrit, platelet count and RSV status. The clinical and laboratory findings were compared between infants who were positive and those who were negative for RSV. The study was approved by the institutional ethics review board.

STATISTICAL ANALYSIS

Data were analyzed with BMDP Software [6]. Continuous variables were compared between the two groups using analysis of variance (ANOVA). Two-tailed Fisher's exact test was used to compare categorical variables. A *P* value of ≤ 0.05 was considered statistically significant. The data were fitted to a stepwise logistic regression model to identify the variables significantly associated with a positive RSV finding. Odds ratios and 95% confidence intervals were calculated.

RESULTS

The study group included 469 infants with bronchiolitis, of whom 363 (77.4%) were positive for RSV infection and 106 (22.6%) were negative. There were 53 (14.6%) preterm infants in the RSV-positive group compared to 14 (13.5%) in the RSV-negative group ($P = 0.875$). The characteristics of the two groups are shown in Table 2. There were no significant differences between the groups for any of the parameters studied, including platelet count.

Thrombocytosis was identified in 181 of the 469 infants (38.6%): 150 of the 363 RSV-positive infants (41.3%) and 31 of the 106 RSV-negative infants (29.2%) ($P = 0.031$). The odds ratio of an infant with thrombocytosis to have a positive RSV infection compared to an infant with a normal platelet count was 1.7 ($P = 0.023$, 95% CI 1.07–2.72). The thrombocytosis was mild (> 500 x 10^9/L to ≤ 700 x 10^9/L) in 134 RSV-positive patients (36.9%) and 25 RSV-negative patients (23.6%) ($P = 0.01$). Moderate thrombocytosis (platelet count >700 x 10^9/L to ≤ 900 x 10^9/L) was detected in 16 and 4 infants (4.4% and 3.8%) in the RSV-positive and negative groups (P = NS), respectively and extreme in none of the children in the RSV-positive group compared to 2 (1.9%) in the RSV-negative group ($P = 0.051$).

On logistic regression analysis, there was no correlation between platelet count and any of the other factors studied including age, gender, days of illness before admission, maximal temperature, bronchiolitis score, hemoglobin or hematocrit levels.

DISCUSSION

Although infection is the most common cause of secondary thrombocytosis in hospitalized children [1], the culprit agents have not been well studied. Our search of the English-language medical literature yielded only one study of a potential viral etiology [2]. In a file review of 345 children with respiratory tract viral infections, Kubota et al. [2] reported a significantly higher mean platelet count in patients positive for RSV infection than in patients with other respiratory viral infections (influenza, measles, adenovirus, and human herpes virus-6). Of all children with thrombocytosis, 82.8% had an RSV infection [2]. However, this study was biased by the significantly lower mean age of the patients with thrombocytosis [2]: the mean age of children with RSV infection was less than one year whereas the mean age of the children with other viral infections was more than 2 years [2]. The known higher frequency of thrombocytosis in infants under age 2 years [1] would account for its higher rate in the RSV group.

In the present prospective study, we found a significantly higher rate of thrombocytosis in the RSV-positive than RSV-

CI = confidence interval

negative groups ($P = 0.031$). Moreover, our findings show that the presence of thrombocytosis in a hospitalized infant aged ≤ 4 months with bronchiolitis increases the likelihood of a positive RSV infection.

The mechanism by which infections cause thrombocytosis is not clear. Some authors have suggested that hypoxia or anemia may play a role [1,2,7]. However, we found no significant difference in bronchiolitis score (which accounted for both respiratory distress and oxygen saturation) between the RSV-positive and the RSV-negative groups, and mean hemoglobin and hematocrit levels were within the normal range for age in all patients.

Other more specific mechanisms by which infections can cause secondary thrombocytosis is elevation of circulating cytokines and hematopoetic factors, including thrombopoietin, interleukin-6, interleukin-8, interleukin-11 and stem cell factor [8]. Thrombopoietin and IL-6 are identified as the most important and potent thrombopoietic factors [9,10]. It has been found that during primary RSV infection, many infants demonstrated RSV-specific cytokine responses [11]. However, other agents apart from RSV can cause bronchiolitis, and investigations on the exact mediators invoked in the pathogenesis of airway inflammation by each agent are still missing.

Complete blood count (and platelet count) is a laboratory test that is routinely performed in our institute on hospitalized infants aged ≤ 4 months with bronchiolitis, mainly to determine white blood cell count and hemoglobin levels. Since we cannot determine RSV status in all cases upon admission, the presence of thrombocytosis may increase the likelihood of RSV positivity and may be helpful in cohorting infants.

Our study is the first to prospectively link a specific viral agent to thrombocytosis in a clinical study. We believe the next step will be to link the specific viral agents causing bronchiolitis to defined inflammatory response and circulating cytokines.

In summary, our prospective investigation indicates that RSV infection in young infants with bronchiolitis is associated with a higher rate of thrombocytosis. This finding may help in cohorting infants hospitalized with bronchiolitis and may lead to further elucidation of the inflammatory process involved in RSV infection in infants. Larger and more specific studies are needed to clarify the specific pathophysiology of thrombocytosis in children and to identify its relationship to the precise causative infectious agents.

IL = interleukin

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