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Importance of Thrombocytosis in the Diagnosis of Asthma and Pneumonia in Children below Five Years

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***Abstract*---**Background: Thrombocytosis is divided into primary and secondary forms. Secondary form is common in children and associated with many conditions as infections, anemia, malignancy, inflammation, hyposplenism and tissue damage. Bacterial or viral infections (acute or chronic) are the most common cause for secondary thrombocytosis at any age during childhood. Objective: To study the role of thrombocytosis in the diagnosis of asthma and pneumonia. A total of 460 children were enrolled in this case-control study Children were categorized into 3 groups, asthma group which included 108 children, pneumonia group which included 262 children and control group which included 90 children. Exclusion criteria were anemia, recent surgery, acute blood loss, malignancy, connective tissue diseases and mixed cases of asthma and pneumonia. Mean platelet count in the pneumonia group was 374000/mm^3 and percentage of children with thrombocytosis was 33%. Mean platelet count in the asthma group was 272000/mm^3 and percentage of

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children with thrombocytosis was 13%. Mean platelet count in the control group was 265000/mm^3 and percentage of children with thrombocytosis was 11.1%. Mean platelet count in pneumonia group was significantly higher than asthma group (p value<0.01) and control group (p value<0.01), but there was no statistical significant difference between asthma group and control group (p value=0.579). Percentage of patients with thrombocytosis in pneumonia group was significantly higher than asthma group (p value<0.01) and control group (p value<0.01), but no statistical significant difference in percentage of thrombocytosis between asthma group and control group (p value=0.691). Thrombocyte count was higher in pneumonia than asthma and control group, so it could be considered as a lab parameter when evaluating children with respiratory complaints.

***Keywords*---**thrombocytosis, asthma, pneumonia, children below five years.

Introduction

Thrombocytosis refers to platelet count >4,00,000/µL in the peripheral blood [1, 2] An elevated platelet count has become an important for differential diagnosis of various pathological and physiological processes [3]. The main function of platelets is to contribute to hemostasis: the process of stopping bleeding at the site of interrupted endothelium, by adhesion, activation and aggregation [4]. Platelets are cytoplasmatic fragments of bone marrow megakaryocytes, with a diameter of 3-5 µm and a volume of 4.5–11 fL. A single megakaryocyte releases 1500–2000 of them to the bloodstream, where they circulate for 7–10 days. Inactivated platelets in the blood are discoid shaped and do not contain a nucleus. Their cytoplasm contains three different types of granules (i.e. alpha granules, dense granules, and lysosomal granules), secretory vesicles that contain pre-formed molecules, and a complex membranous system [5].

Platelets are derived from proplatelets which represent long protrusions of the mature magakaryocyte cytoplasm [6]. Thrombopoietin regulates the differentiation of megakaryocytes and platelets. Thrombopoietin is produced in the liver, kidney and striated muscle and bone marrow stromal cells. In the liver, its production is augmented by interleukin 6 [7]. The cytokine thrombopoietin stimulates platelet production through ligation of its cognate surface receptor c-Mpl. Other signals also contribute to thrombopoiesis including stem cell derived factor 1, integrins and platelet factor 4 [8]. Thrombocytosis is classified according to its origin into primary and secondary forms. Primary (clonal) thrombocytosis is a myeloproliferative disorder, caused by abnormal and uncontrolled expansion of haematopoietic cells [3]. Secondary (or reactive) thrombocytosis is due to a variety of underlying conditions like infection, inflammation, iron deficiency, tissue damage, hemolysis, severe exercise, malignancy, hyposplenism, and other causes of an acute phase response. Bacterial or viral infections (acute or chronic) are the most common cause for secondary thrombocytosis at any age during childhood. Within this group, infections of the respiratory tract account for 60–80% of secondary thrombocytosis, followed by infections of the gastrointestinal and

urinary tract [9]. Pneumonia is defined as a lower respiratory tract infection typically associated with fever, respiratory symptoms, and evidence of parenchymal involvement by either physical examination or the presence of infiltrates on chest radiography. Pathologically, it represents an inflammatory process of the lungs, including airways, alveoli, connective tissue, visceral pleura, and vascular structures. Radiologically, pneumonia is defined as an infiltrate on chest radiograph in a child with symptoms of an acute respiratory illness [10]. A complete blood cell count with differential does not allow differentiation among bacterial, atypical, or viral origins or dictate management, particularly in the outpatient setting. A complete blood cell count with differential is typically performed in children who are candidates for hospitalization [11, 12]. Peripheral eosinophilia suggests Chlamydia trachomatis in infants with afebrile pneumonia. Asthma is a chronic inflammatory condition of the lung resulting in episodic airflow obstruction [13]. Asthma comprises a range of heterogeneous phenotypes that differ in presentation, etiology and pathophysiology. The risk factors for each recognized phenotype of asthma include genetic, environmental and host factors [14]. To study the role of thrombocytosis in the diagnosis of asthma and pneumonia.

Method

A total of 460 children below five years were enrolled in this case- control study conducted at Babil Gynecology and Children's Teaching Hospital in Hilla / Iraq from February 2017 to December 2017. Children were categorized in to 3 groups, the 1st group included 108 patients with asthma, the 2nd group included 262 patients with pneumonia and the 3rd group is the control group which included 90 healthy children. We choose age matched children. Exclusion criteria were anemia, recent surgery, acute blood loss, malignancy connective tissue disease and mixed cases of asthma and pneumonia. History was taken from children guardians for elevated temperature, cough, difficult breathing, other respiratory symptoms, associated systemic symptoms, duration of symptoms, and previous history of medical seek, medical conditions as malignancy or connective tissue disease, history of recent surgery or acute blood loss, drug history, family history of asthma and atopy and history of sensitization to specific allergen. Physical examination was done for vital signs, signs of respiratory distress, auscultatory findings, other associated physical findings and oxygen saturation. The complete blood count was measured from the collected blood samples using a Ruby® CELL-DYN automatic hematologic analyzer (Abbot Diagnostic Division, USA) and the results were recorded in a formula sheet for data analysis. Platelet count >400000/mm^3 considered as thrombocytosis [1, 2] The lower normal level of hemoglobin considered as 10.5 g/dl in children aged from nine months to two years and 11.5 g/dl in children aged from two to five years [15]. The data were collected, organized and tabulated using the SPSS software version 25. The results were expressed in form of number, range, mean±standard deviation and number and percentage of thrombocytosis. Independent t-test used to analyze the difference in means between the three groups. Fisher's exact used to evaluate difference in percentage of thrombocytosis between the three groups. P value <0.05 was considered to be statistically significant.

Results

A total of 460 children had been evaluated in this case control study, 262 children with pneumonia, 108 children with asthma and 90 healthy children as a control group. For patients with asthma, 59 patients (54.6%) were males and 49 patients (45.4%) were females. Ranging between 9-59 months. Mean of age was 32.4 months. From total asthmatic patients, 14/108 patients (13%) had thrombocytosis at the time of diagnosis. Hematological findings in patients with asthma are demonstrated in (table 1).

(Table 1). Hematological findings in patients with asthma

Data	Range	Mean ± SD
Hemoglobin level (g/dl)	10.5-16	12.9 ± 1.2
WBC count (cell/mm³)	4100-16000	9300 ± 2900
Platelet count (cell/mm³)	152000-491000	272000 ± 98000

For patients with pneumonia, 136 patients (51.9%) were males and 126 (48.1%) patients were females. Ranging between 9-59 months. Mean of age was 29 months. From the total patients diagnosed with pneumonia, 87/262 patients (33%) had thrombocytosis at time of diagnosis. Hematological findings in patients with pneumonia are demonstrated in (table 2).

(Table 2). Hematological findings in patients with pneumonia

Data	Range	Mean±SD
Hemoglobin level (g/dl)	10.6-16	12.6±1.9
WBC count (cell/mm³)	4900-19200	12200±3100
Platelet count (cell/mm³)	158000-587000	374000±87000

For the control group, 48 children (53.3%) were males and 42 children (46.7%) were females. Ranging between 5-59 months. Mean of age was 30.5 months. From the control group, 10/90 children (11.1%) had thrombocytosis Hematological findings are demonstrated in (table 3).

(Table 3). Hematological findings in the control group

Data	Range	Mean ± SD
Hemoglobin level (g/dl)	10.8 - 15.3	12.7 ± 1.3
WBC count (cell/mm³)	4500 - 14600	8600 ± 2600
Platelet count (cell/mm³)	154000 - 472000	265000 ± 88000

By comparing means of parameters between asthmatic patients and control group, there was no statistical significant difference between them, as shown in (table 4).

(Table 4). Comparison between means of findings in asthmatic patients and control group

Data	Mean ± SD (asthma group)	Mean ± SD (control group)	P value
Hemoglobin level (g/dl)	12.9±1.2	12.7±1.3	0.106
WBC count (cell/mm^3)	9300±2900	8600±2600	0.087
Platelet count (cell/mm^3)	272000±98000	265000±88000	0.579

There was no statistical significant difference in percentage of thrombocytosis between asthma and control group (p value = 0.691). Regarding comparison between means of parameters in pneumonia group and control group, there was statistical significant difference between mean of platelet count and WBC count and no statistical significant difference between mean of age and hemoglobin level in the two groups, as shown in (table 5).

(Table 5). Comparison between means of findings in pneumonia group and control group

Data	Mean ± SD (pneumonia group)	Mean ± SD (control group)	P value
Hemoglobin level (g/dl)	12.6±1.9	12.7±1.3	0.626
WBC count (cell/mm^3)	12200±3100	8600±2600	< 0.01
Platelet count (cell/mm^3)	37400±87000	265000±88000	< 0.01

There was high significant difference between percentage of thrombocytosis in pneumonia group and control group (p value < 0.01). Regarding comparison between means of parameters in asthma group and pneumonia group, there is statistical significant difference between mean of platelet count and WBC count and no statistical significant difference between mean of hemoglobin level and age in the two groups, as shown in (table 6).

(Table 6). Comparison between mean of findings in pneumonia group and asthma group

Data	Mean ± SD pneumonia group	Mean ± SD asthma group	P value
Hemoglobin level (g/dl)	12.6±1.9	12.9±1.2	0.16
WBC count	12200±3100	9300±2900	< 0.01

(cell/mm^3)			
Platelet count (cell/mm^3)	374000±87000	272000±98000	< 0.01

There is high significant difference between percentage of thrombocytosis in pneumonia group and asthma group (p value < 0.01).

Discussion

In the current study, we found that mean thrombocyte count in patients with pneumonia was significantly higher than control group (p value < 0.01) and asthma group(p value < 0.01), but there was no statistical significant difference between patients with asthma and control group (p value = 0.579). Otherwise, the percentage of patients with pneumonia and had thrombocytosis was significantly higher than control group (p value < 0.01) and asthma group (p value < 0.01), but there was no statistical significant difference between asthmatic patients and control group (p value = 0.691). This could be explained by that the increase thrombocyte count during an infectious process is related to increased endogenous levels of several cytokines, such as thrombopoietin (TPO), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-1alpha (IL-1a) and tumor necrosis factor alpha (TNF-a) [16]. Also platelets have been increasingly recognized as an important component of innate and adaptive immunity. Platelets contain antimicrobial peptides that act against a broad range of pathogens. After are activated, they accumulate at the site of infection to produce direct contact between their antimicrobial peptides and invading bacteria. Platelets can internalize microorganisms into phagosome-like vacuoles, enhancing pathogen clearance. Antimicrobial peptides exert a rapid, potent, and direct antimicrobial effect that contributes to limiting the infection [17]. In a study done by Aydemir et al [18] in Antalya and Istanbul in Turkey, they found that the mean thrombocyte count and number of patients with thrombocytosis was higher in cases with pneumonia and bronchiolitis than asthmatic patients were. These findings are agree with the current study. In other study done by Bilavsky E et al [19], they found a significant relation between thrombocytosis and RSV bronchiolitis that is similar to the current study about the relation between respiratory infections and thrombocytosis. In a study done by Yang M et al [20], they reported increase thrombopoietin and thrombocyte count in the SARS disease and this result goes with this study. The underlying inflammatory stimulus may increase the amount of the thrombopoietin produced in the liver. Thrombopoietin plays a key role in the course of megakaryocyte differentiation and proliferation and this will increase thrombocyte count [21]. Vlacha V et al [22] reported that thrombocytosis occur in serious lower respiratory tract infections and this goes close with the current study. In the studies that were done by Bilavsky E et al [19], Yang M et al [20] and Vlacha V et al [22], the thrombocytosis which occurs due to a pulmonary infection was studied but with no comparison with the other pulmonary diseases. Also we found that mean WBC count in pneumonia group was significantly higher than control group (p value < 0.01) and asthma group (p value < 0.01), but there was no statistical significant difference in mean WBC count between asthma group and control group (p value = 0.087). Leukocytosis could be caused by infection, inflammatory diseases and malignancy [23]. We excluded malignant and inflammatory conditions from our study so leukocytosis in our study is mostly

due to infection (pneumonia). Our results showed no statistical significant difference in mean hemoglobin level between the three groups included in the study. Anemia is one of the causes of thrombocytosis [9] but we excluded anemic patients from our study.

Conclusion

The mean thrombocyte count and percentage of thrombocytosis in children with pneumonia was significantly higher than that seen in children with asthma and control groups. These results were comparable to results from other studies done in Asia and Europe.

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