ORIGINAL RESEARCH

Thrombocytosis in Children: Clinico-Hematological Profile from tertiary care centre in north India – One year prospective study

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Received: 12 March, 2023 Accepted: 18April, 2023

ABSTRACT

Aim: To evaluate the thrombocytosis in Pediatric Patients with clinical and hematological characteristics at a tertiary care center in north India.

Materials and Methods: The study included all children between the ages of 0 -16 who were attending pediatrics and pediatric super specialty clinics, both in outpatient and inpatient settings. The parameters of complete blood counts, including hemoglobin, red cell indices, and platelet indices PDW, MPV, and P-LCR, were observed. Additional biochemical parameters, including C-reactive protein, erythrocyte sedimentation rate, serum iron profile, blood culture, and urine culture, were documented in accordance with the clinical indications for each individual case.

Results: It was observed that the largest proportion of participants fell within the 0-4 years age group, accounting for 45% of the total sample. It was observed that 72.5% of the children exhibited mild thrombocytosis, while moderate and severe thrombocytosis were observed in 20.83% and 6.67% of the children, respectively. The etiology was found to be secondary or reactive in 98.33% of cases, with only two cases of primary thrombocytosis observed. Two cases of Philadelphia positive pediatric chronic myeloid leukemia (CML) exhibited primary or clonal thrombocytosis. The primary etiology of secondary thrombocytosis was found to be infection, accounting for 41.67% of cases. Among these cases, respiratory tract infections were responsible for the highest proportion, specifically 19.17%. The prevalence of iron deficiency anemia (IDA) was observed to be 12.5%, while the occurrence of IDA in conjunction with concurrent infection was found to be 10.83%. A prevalence rate of 9.17% was observed for hemoglobinopathies that were accompanied by secondary thrombocytosis. The second largest group consisted of cases of drug-induced thrombocytosis, accounting for 13.33% of the total. A notable observation in this study was the inverse relationship between platelet counts and mean platelet volume (MPV), as evidenced by the significant negative correlation ($P<0.05$) reported.

Conclusion: The occurrence of thrombocytosis in pediatric patients is primarily attributed to secondary causes, while primary thrombocytosis, specifically clonal thrombocytosis, is exceedingly uncommon in this population. In children, infections are the primary cause of secondary thrombocytosis, which is typically a temporary condition and does not have significant clinical consequences.

Keywords: Thrombocytosis, Infection, Mild, Severe.

Introduction

Platelets play a crucial role in upholding the structural integrity of the vascular endothelium and regulating hemostasis by initiating the formation of platelet plugs to prevent excessive bleeding from microvasculature. The typical range for platelet count is between 150,000 and 450,000 per cubic millimeter. Platelets are derived from megakaryocytes and have a lifespan of approximately 7-10 days. Their primary role is to regulate the processes of hemostasis and thrombosis.[1,2] Platelets are small, disc-shaped cellular fragments that derive from megakaryocytes,

which are formed in the hematopoietic lineage. The process of platelet production from megakaryocytes is a systematic and regular phenomenon that is widely believed to take place within the bone marrow. Throughout its typical life cycle, there is a reduction in platelet size, resulting in younger platelets being larger in comparison to older platelets. Platelets, upon reaching the culmination of their life cycle subsequent to complete activation, participate in the process of clot formation within blood vessels [3]. Subsequently, neutrophils and macrophages undertake the task of eliminating these platelets from the blood vessels, after which they are transported to the spleen for subsequent removal from the body [1]. Thrombocytosis refers to a condition in which the quantity of platelets surpasses the normal count by a magnitude of 2 standard deviations (SD) based on age-specific norms, or when the platelet count exceeds 450,000/mm3. This disorder of platelet count can be attributed to various etiological factors and is frequently encountered in routine clinical settings. Thrombocytosis is classified into two categories, primary (essential) and secondary (reactive), based on the underlying abnormality. Primary thrombocytosis is infrequently encountered and atypical in pediatric patients, primarily due to the limited recognition of genetic mutations and clinical data. Primary thrombocytosis is a condition characterized by the excessive production of platelets, which arises from either monoclonal or polyclonal abnormalities in the hematopoietic cells or biological irregularities in thrombopoietin (Tpo), a key regulator of megakaryopoiesis. Secondary or reactive thrombocytosis is typically a temporary condition that arises as a result of increased production of platelets, known as megakaryopoiesis, which is associated with abnormalities in the blood or other bodily systems. The distinction between primary and secondary thrombocytosis holds significance due to its implications for the assessment, prognosis, and management of the condition [2,4]. Secondary thrombocytosis is the predominant etiology of thrombocytosis in both adult and pediatric populations, accounting for approximately 88-97% of cases in adults and nearly 100% in children. Reactive thrombocytosis is associated with a range of medical conditions, including the inflammatory process, in which platelets are involved as part of the acute phase response. This phenomenon is frequently observed in pediatric populations, and its etiology can be attributed to either innate or adaptive immunity, or alternatively, to the higher susceptibility of children to infections. In addition to inflammation and infection, thrombocytosis can also be caused by acute bleeding, iron deficiency anemia, or malignancy. Following the surgical removal of the spleen (splenectomy), there is an initial increase in platelet count within the first week, which subsequently returns to baseline levels after a period of approximately three months [5-7]. The utilization of hematology auto-analyzers and the improved precision of blood cell counters have led to a significant rise in the identification of thrombocytosis, particularly in cases of mild severity. Nevertheless, this frequently observed result in a routine hemogram often prompts inquiries among pediatricians regarding its potential etiology and clinical ramifications. Taking into consideration this particular observation, the present study was conducted to evaluate the prevalence of thrombocytosis among pediatric patients, while also investigating the underlying causes and examining its association with platelet parameters.

Materials and Methods

The present study is a prospective observational investigation conducted at a tertiary health center. The study included all children between the ages of 0 to 16 who were attending pediatrics dept. both in outpatient and inpatient settings. The study excluded cases in which the workup was incomplete and repeat hemograms were performed on the same patients. Routine A comprehensive blood analysis, known as a complete hemogram, was conducted using a 2 ml sample of blood treated with ethylene diaminete traacetic acid. This analysis was performed using a 6 part differential hematology Autoanalyzer (XN-1000). Subsequently, cases exhibiting thrombocytosis were examined through the evaluation of peripheral smears. After the confirmation of the diagnosis through smear analysis, the patient's case history, presenting signs and symptoms, as well as their medical and drug history, were documented. The parameters of complete blood counts, including hemoglobin, red cell indices, and platelet indices PDW, MPV, and P‑LCR, were observed. Additional biochemical parameters, including C-reactive protein, erythrocyte sedimentation rate, serum iron profile, blood culture, and urine culture, were documented in accordance with the clinical indications for each individual case. According to Dame and Sutor [8], thrombocytosis was classified into four grades: mild (greater than 500 × 103/µl to 7 × 103/µl), moderate (greater than 7 × 103/µl to 9 × 103/µl), severe (greater than 900 × 103/µl), and extreme (greater than 1000 × 103/µl). The etiology of the cases was determined through the analysis of clinical parameters, relevant laboratory data, and subsequent categorization into subgroups. The study excluded any duplicate hemograms from the same patients. The study received approval from the institutional ethical committee. The study obtained informed consent from the parents of all patients who were included in the research. was conducted using SPSS version 20. The mean, standard deviation, and P-value were computed. A significance level of $P < 0.05$ was deemed to indicate statistical significance.

Results

A cohort of 120 pediatric patients exhibited thrombocytosis. The age range of the participants in this study spanned from infancy to adolescence, encompassing individuals between the ages of 0 and 16 years. It was observed that the largest proportion of participants fell within the 0-4 years age group, accounting for 45% of the total sample. The male to female ratio was reported as 2.16:1. In Table 1, it was observed that 72.5% of the children exhibited mild thrombocytosis, while moderate and severe thrombocytosis were observed in 20.83% and 6.67% of the children, respectively. The etiology was found to be secondary or reactive in 98.33% of cases, with only two cases of primary thrombocytosis observed [Table 2]. Two cases of Philadelphia positive pediatric chronic myeloid leukemia (CML) exhibited primary or clonal thrombocytosis. No instances of Essential Thrombocytosis (ET) encounters were observed. The etiological spectrum of secondary thrombocytosis exhibits a wide range of causes. The primary etiology of secondary thrombocytosis was found to be infection, accounting for 41.67% of cases. Among these cases, respiratory tract infections were responsible for the highest proportion, specifically 19.17%. The prevalence of iron deficiency anemia (IDA) was observed to be 12.5%, while the occurrence of IDA in conjunction with concurrent infection was found to be 10.83%. A prevalence rate of 9.17% was observed for hemoglobinopathies that were accompanied by secondary thrombocytosis. The second largest group consisted of cases of drug-induced thrombocytosis, accounting for 13.33% of the total. To examine the correlation between platelet indices and the severity of thrombocytosis, the cases were divided into three distinct categories (mild, moderate, and severe). Subsequently, the mean value, standard deviation, and P value were computed and presented in Table 3. Upon analysis, it was observed that there exists an inverse relationship between the platelet indices and the degree of thrombocytosis. A notable observation in this study was the inverse relationship between platelet counts and mean platelet volume (MPV), as evidenced by the significant negative correlation ($P<0.05$) reported in Table 3. The mean platelet distribution width (PDW) of children diagnosed with mild thrombocytosis was found to be 11.15±1.24, while children with moderate thrombocytosis had a mean PDW of 10.59±1.13. A comparable finding was observed in relation to P-LCR, with the mean P-LCR values being 24.58±2.69 and 21.41±2.44 for cases of mild and moderate thrombocytosis, respectively. In the third category of severe thrombocytosis, the average values for mean platelet volume (MPV), platelet large cell ratio (P-LCR), and platelet distribution width (PDW) were 9.22±0.96, 21.14±1.98, and 10.21±1.64, respectively.

Table 1: Grades of thrombocytosis with age groups

Age	Grades of thrombocytosis			
	Mild	Moderate	Severe	Total
0-4	37(68.52)	15 (27.78)	2(3.70)	54(45)
4-8	23 (76.67)	4 (13.33)	3(10)	30(25)
8-12	15 (75)	3 (15)	2(10)	20(16.67)
12-16	12 (75)	3 (18.75)	1(6.25)	16(13.33)
Total	87(72.5)	25(20.83)	8(6.67)	120(100%)

Table 2: Etiology of thrombocytosis

	Number	**Percentage**
Primary	**2**	**1.67**
Reactive	**118**	**98.33**
Anemia Infection and anemia	**13**	**10.83**
Iron deficiency	**15**	**12.5**
Infection alone	**50**	**41.67**
Respiratory tract infection	**23**	**19.17**
Urinary tract infection	**8**	**6.67**
Bacteremia	**3**	**2.5**
Gastrointestinal infection	**13**	**10.83**
CNS infection	**3**	**2.5**
Hemoglobinopathies	**11**	**9.17**
Trauma/burn	**1**	**0.83**
Surgery	**12**	**10**
Drugs	**16**	**13.33**

Table 3: Correlation of platelet indices with Severity of thrombocytosis

Grades of thrombocytosis	PDW	MPV	P-LCR
Mild	11.15± 1.24	10.02±1.09	24.58±2.69
Moderate	10.59± 1.13	9.63±1.44	21.41±2.44
Severe	10.21± 1.64	9.22±0.96	21.14±1.98

Discussion

Thrombopoietin (Tpo) serves as the principal modulator of platelet generation in humans, predominantly manifested in the liver, and to a lesser degree in the kidneys, bone marrow, and other bodily tissues. The c-mpl receptor, which is expressed on pluripotent megakaryocytes, platelets, and endothelial cells, plays a role in facilitating the commitment of hematopoietic stem and progenitor cells towards platelet-specific differentiation. The C-mpl receptors typically facilitate the cellular absorption and internalization of circulating Tpo. The expression of hepatic Tpo remains unaltered in the presence of thrombocytopenia. Thrombocytopenia resulting from platelet destruction is associated with normal Tpo serum concentrations, whereas a decrease in thrombopoiesis is linked to elevated Tpo serum concentrations. Thrombocytosis in pediatric patients predominantly manifests as a reactive or secondary condition, typically arising as a consequence of an acute phase reaction. The incidence of thrombocytosis in hospitalized children ranges from 6% to 15%, but this estimate may vary due to differences in how thrombocytosis is defined, the specific study settings, and the prevalence of underlying factors such as infections, anemia, and malignancies.[8] Transient and secondary manifestations frequently occur as a result of underlying inflammatory conditions, and subsequently resolve upon treatment of the root cause. The frequency of infections is greater in children compared to adults, primarily due to the immaturity of their innate and/or adaptive immune systems, as well as their increased exposure to infectious agents.[9] In contrast, primary thrombocytosis is a condition that is exceptionally uncommon among pediatric populations. The pathomechanism underlying the primary form is characterized by the spontaneous generation of megakaryocytic progenitors and heightened responsiveness to thrombopoietin (Tpo). In the secondary form, the production of hepatic thrombopoietin (Tpo) is enhanced as an acute response to a range of conditions.[9] Thrombocytosis was observed in 12.5% of the cases in our study. This finding aligns with previous research conducted by Dame and Sutor.[8] The incidence of reactive thrombocytosis in childhood varies depending on age, with the highest occurrence observed in children up to 2 years of age.[7] Our study also observed a similar trend, with the highest incidence of thrombocytosis occurring in the age group of 0-4 years, accounting for 45% of cases. The literature review indicates that there is a slight elevation in platelet counts, reaching up to 7,00,000/µL, in approximately 72% to 86% of cases. Additionally, moderate and severe thrombocytosis are observed in approximately 6% to 8% and 2% to 3% of children, respectively.[8] The current study observed mild thrombocytosis in 72.5% of cases, while moderate and severe thrombocytosis were observed in 20.83% and 6.67% of cases, respectively, consistent with findings reported in previous studies. The prevalence of newly diagnosed primary thrombocytosis in pediatric patients is approximately 1 in 10 million, which is significantly lower compared to the adult population, with a difference of approximately 60-fold.In the present study, there were no observed instances of essential thrombocytosis (ET). Two cases of Philadelphia-positive pediatric chronic myeloid leukemia (CML) were identified. Additionally, it was observed that as age increased, the severity of thrombocytosis decreased. Among individuals aged >12 years, mild cases accounted for 86.67%, while among those aged 0-4 years, mild cases accounted for 45%. This finding aligns with the literature review referenced.[8] According to the findings of a study conducted by Dame and Sutor, the primary etiology of reactive thrombocytosis in childhood is attributed to bacterial or viral infections, whether acute or chronic in nature.[8] Within this particular cohort, it has been observed that respiratory tract infection is the prevailing ailment, with gastrointestinal and urinary tract infections subsequently following suit in terms of frequency.[11,12] The etiological spectrum observed in our study exhibited similarities, with infections accounting for 41.67% of cases. Among these infections, respiratory tract infections were the most prevalent, followed by gastrointestinal infections and urinary tract infections. Our center observed a relatively higher incidence of drug-induced thrombocytosis (13.33%) in patients who were administered corticosteroids and chemotherapeutic agents such as vincristine. The majority of these instances involved patients diagnosed with Acute Lymphoblastic Leukemia who were undergoing treatment with vincristine or steroid therapy. These patients exhibited reactive thrombocytosis on multiple occasions. There has been a suggestion that vincristine may have the effect of reducing platelet utilization, leading to an extended life span for platelets and an increase in their production within the bone marrow.[13] The elevated figure can be ascribed to the hospital's role as a specialized facility for the referral and treatment of hemato-oncology cases. During the course of treatment, two instances of

immune thrombocytopenia (ITP) treated with steroid therapy were observed to exhibit a subsequent occurrence of rebound thrombocytosis. The administration of corticosteroids has been observed to induce a temporary increase in platelet count, known as transient thrombocytosis, through the liberation of platelets stored in the spleen into the systemic circulation.[14] Within the realm of immune thrombocytopenia (ITP), the process of megakaryopoiesis undergoes acceleration as a direct reaction to the immune-mediated destruction of platelets. In certain instances, thrombocytosis can occur during therapy when compensatory mechanisms result in excessive platelet production during a phase characterized by reduced or normalized platelet destruction. Yohannan et al. (15) reported three cases of immune thrombocytopenia (ITP) in which rebound thrombocytosis occurred after steroid treatment. Secondary thrombocytosis, consisting of iron deficiency anemia (IDA) alone and IDA with concurrent infections, accounted for 12.5% and 10.83% of cases, respectively. As per the findings of C. Sandoval, it has been determined that IDA continues to be the prevailing noninfectious etiology leading to reactive thrombocytosis.[16] In our study, a prevalence of 9.17% was observed for the occurrence of hemoglobinopathies in association with reactive thrombocytosis. Yadav et al. (year) additionally documented seven instances of thalassemias accompanied by reactive thrombocytosis.[17] The higher prevalence of hemoglobinopathies in this particular case can be attributed to the fact that the center in question serves as a referral center for individuals with hemoglobinopathies. The platelet indices were assessed in relation to the severity of thrombocytosis. There was a negative correlation observed between the degree of thrombocytosis and the values of mean platelet volume (MPV), platelet distribution width (PDW), and platelet-large cell ratio (P-LCR). In their study, Subramaniam et al. conducted a comparison between platelet indices and the degree of thrombocytosis. They observed a weak but statistically significant negative correlation between the mean platelet volume (MPV) and the degree of thrombocytosis.[18] There were no instances of thromboembolic episodes observed in any of the cases. Nevertheless, this study was subject to a number of limitations. In certain instances, it was not feasible to monitor the impact of treatment for underlying diseases on the response of thrombocytosis. Additionally, the platelet indices in reactive thrombocytosis could not be compared to those in primary thrombocytosis, with only a single case available for analysis in our series. A comprehensive study is currently underway at a hospital setting to examine the association between inflammatory markers and the extent of thrombocytosis. Additionally, the study aims to observe the changes in thrombocytosis and platelet indices in response to treatment.

Conclusion

The occurrence of thrombocytosis in pediatric patients is primarily attributed to secondary causes, while primary thrombocytosis, specifically clonal thrombocytosis, is exceedingly uncommon in this population. In children, infections are the primary cause of secondary thrombocytosis, which is typically a temporary condition and does not have significant clinical consequences. Nevertheless, in the absence of a secondary etiology for the elevated platelet count or its persistence following treatment of the primary cause, it is imperative to conduct an investigation into the presence of an underlying primary thrombocytosis.

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