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Essential Thrombocythemia and Reactive Thrombocytosis in Children

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Abstract

Background: Thrombocytosis is defined as an increased number of peripheral blood platelets. With respect to this value, it is graded as: mild thrombocytosis with platelet number 500-700 G/L; moderate thrombocytosis with platelet number 700-900 G/L; severe thrombocytosis with platelet number >900 G/L and extreme thrombocytosis if the platelet count is > 1000 G/L.

Objective: Analysis of epidemiology, etiology and clinical course of primary and secondary thrombocytosis in children.

Methods: All consecutive children hospitalized in pediatric, hematology and oncology ward during 48 months were potential subject of this retrospective analysis. All children with at least one platelet count above 500 G/L were included into the study.

Results: Thrombocytosis was observed in 628/12910 (4,86%) hospitalizations. It was diagnosed as mild in 83,9% of cases; moderate and severe in 14,0%, and extreme in 2,1% cases. The most frequent cause of thrombocytosis were infections and iron deficiency anemia, as well as bone marrow regeneration after chemotherapy administered due to malignancy and patients after splenectomy. It was found that primary thrombocythemia is a very rare disease in children and constitutes only 0,47% off all cases of thrombocytosis, and 0,02% of all hospitalizations pediatric, hematology and oncology ward. Clinical course of secondary thrombocytosis is usually symptomless with fast normalization of platelet count after underlying condition has been cured.

Conclusions: Secondary thrombocytosis occurs in nearly 5% of hospitalized children, while primary thrombocythemia is a very rare disease of childhood. There are no recommendations for routine prophylaxis with thrombolytic agents or inhibitors of platelet aggregation in secondary thrombocytosis.

Keywords: *primary thrombocytosis; secondary thrombocytosis; children; JAK mutation*

Introduction

Thrombocytosis is defined as an increased number of peripheral blood platelets. This definition is the same for children and adults. The proper platelet number is a value 150-450 G/L (109/l.). These values are generally considered normal in healthy newborns, infants, children and adolescents [1]. In the literature we can find different divisions of thrombocytosis. For the purpose of this paper, one made a division based on the number of platelets (Sutor, 1999); we can distinguish: moderate thrombocytosis with platelet number 700-900 G/L, severe thrombocytosis with platelet number > 900 G/L and extreme thrombocytosis with platelet number > 1000 G/L [1].

Due to the etiology, types of thrombocytosis can be divided into primary, secondary and alleged. Primary thrombocytosis is classified as myeloproliferative disorder. It is characterized by platelet number > 450 G/L and tendency of the occurrence of both bleeding and thrombotic incidents [2, 3]. Secondary thrombocytosis is a result of excessive megacariopoyesis and thrombopoiesis in the course of various disorders, both hematologic and non-hematologic. The most common causes of secondary thrombocytosis are shown in Table 1.

Etiological factor
1. Infections
• Respiratory tract
• Gastrointestinal tract
• Urinary tract
• Otitis media
• Inflammation of lymph nodes
• Bakteraemia
2. Oncological/ Hematologic
• Cancers
• Anemia
• State after splenectomy
3. Other
• Systemic diseases
• Atopic dermatitis

Table 1: *Causes of secondary thrombocytosis*

Alleged thrombocytosis is defined as an apparent increase in the number of platelets, due to the presence of fragments of leukocytes, erythrocytes or microspherocytes. To exclude this type of irregularity, it is necessary to perform a smear and an examination of peripheral blood in the light microscope.

The study aims at analyzing the epidemiology, etiology and clinical course of primary and secondary thrombocytosis in children.

Patients and Methods

Retrospective analysis was performed in all children hospitalized in the Clinic, during subsequent 48 months (the years 2010-2013). The study was participated by all patients who were found thrombocytosis over 500 G/L in at least one blood cell count.

After elimination, based on the history, of the relationship of thrombocytosis with taken medication (corticosteroids, certain antibiotics, cyclorporine) and after elimination of the foci of infection, anemia, cancer in physical examination and additional studies; in case of suspicion of primary thrombocytosis (idiopathic), one performed bone marrow puncture under general anesthesia, as well as myelogram and cytogenetic and molecular examination of bone marrow for the presence of the JAK2 V617F mutation. In case of suspicion of secondary thrombocytosis, one performed examinations for etiological factors listed in Table 1. Clinical course was analyzed with particular regard to the possibility of thromboembolic complications.

Statistical Analysis: Differences in the prevalence of categorical characteristics between groups were compared by chi-square test.

Results

Epidemiology: In the years 2010-2013, for the total number of 12910 patients hospitalized in the Clinic, 628 (4.86%) were diagnosed with thrombocytosis. In 83.9% of cases it was mild, in 14.0% it was moderate and severe, and in 2.1% it was extreme.

Age	Total	Mild thrombocytosis	Moderate and severe thrombocytosis	Extreme thrombocytosis
0-2 years of age	371 (59.07%)	318 (50.64%)	49 (7.80%)	4 (0.64%)
2-5 years of age	96 (15.28%)	81 (12.90%)	14 (2.23%)	1 (0.16%)
5-10 years of age	59 (9.39%)	53 (8.44%)	4 (0.64%)	2 (0.32%)
>10 years of age	103 (16.4%)	75 (11.94%)	21 (3.34%)	6 (0.96%)
Total	628 (100%)	527 (83.91%)	88 (14.01%)	13 (2.07%)

Table 2: *Frequency of thrombocytosis in age groups*

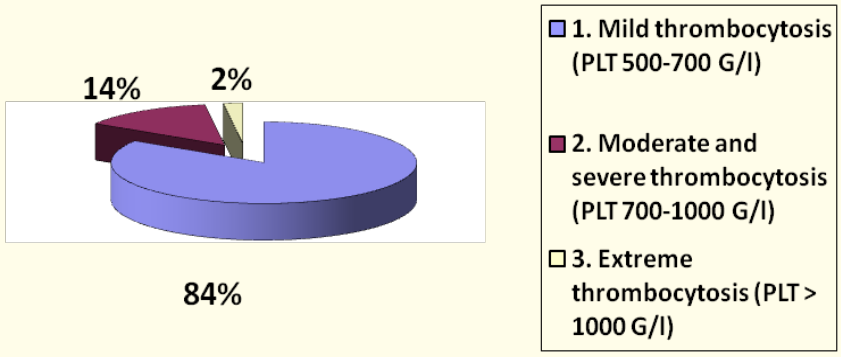

Figure 1: *Distribution of secondary thrombocytosis with respect to staging.*

The occurrence of thrombocytosis showed the dependence of age. The diagnosis was most common made in children under 2 years of age ($p<0.001$), including the most often in the group of mild to moderate thrombocytosis ($p<0.001$) (Tab. 2). Extreme thrombocytosis constituted 4/371 (1.08%) of cases in children to 2 years of age; 1/96 (1.04%) in children aged 2-5 years, 2/59 (3.39%) in children aged 5-10 years and the most often, because 5/103 (5.83%) among children over the age of 10 years ($p<0.01$).

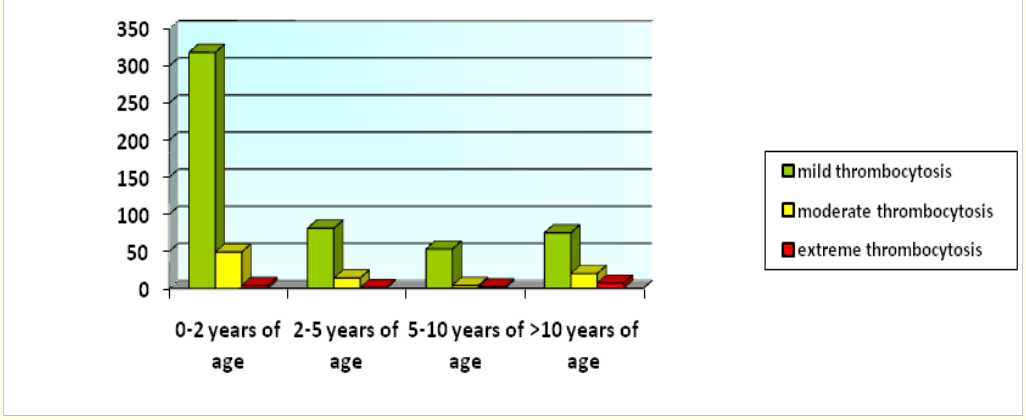

Figure 2: *Episodes of thrombocytosis in hospitalized patients with respect to age groups.*

Causes of Thrombocytosis: The most often causes leading to thrombocytosis in children hospitalized in the Clinic were inflammatory processes. Among the infections, one mainly observed respiratory diseases (pneumonia, bronchiolitis and bronchitis), urinary tract infection, sepsis, gastrointestinal tract infection, as well as inflammations of bones, joints and soft tissues, and anemia due to iron deficiency.

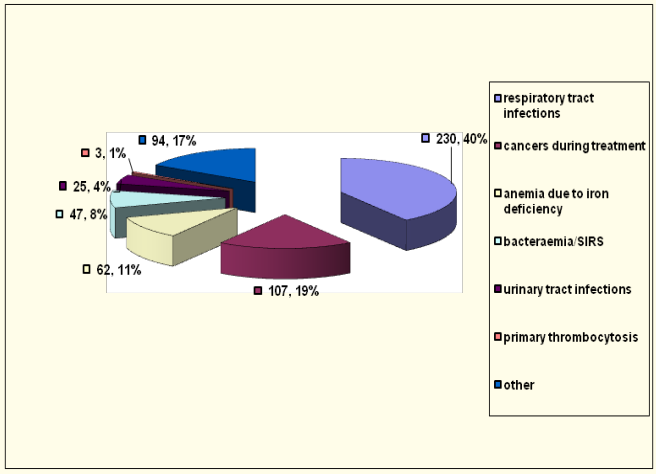

Figure 3: *The most frequent causes of thrombocytosis.*

Causes of thrombocytosis	Mild Thrombocytosis PLT 500-700G/L	Moderate and severe thrombocytosis PLT 700-1000G/L	Extreme thrombocytosis PLT>1000G/L
Respiratory tract infections	200	28	2
Cancers during treatment	100	6	1
Anemia due to iron deficiency	52	8	2
Bacteraemia/SIRS	31	14	2
Urinary tract infections	21	4	0
Solid tumors (neuroblastoma, sarcoma, nephroblastoma, brain tumors)	18	1	0
State after splenectomy (trauma, spherocytosis, thrombocytopenia)	14	1	0
Hemolytic anemias	13	3	0
Gastrointestinal tract infections (mouth, stomach, intestines, appendicitis)	10	3	1
Inflammation of bones and/or joints	7	4	0
Inflammation of lymph nodes	8	1	0
Atopic dermatitis	6	1	2
Immune disorders	9	0	0
Tumors of the liver (hepatoblastoma, metastasis, focal nodular hyperplasia)	2	4	1
Urosepsis	4	2	0
Inflammation of soft tissues (skin, subcutaneous tissue)	3	2	1
Hemangiomas	4	1	0

Otitis media	3	2	0
Inflammation of pancreatitis and liver	3	1	1
Hemophilia A, B (intraarticular hemorrhage)	3	0	0
Neuroinfections	2	0	0
Systemic diseases (lupus)	2	0	0
Stevens-Johnson syndrome	2	0	0
Primary thrombocytosis	1	2	0
Other	9	0	0

Table 3: *Causes of thrombocytosis in children treated in the department.*

In view of the Clinic's profile, a significant percentage were hospitalizations of patients treated for cancer. Only 3 patients suffered from thrombocytosis were diagnosed with the V617F JAK mutation (Table 3).

Idiopathic Thrombocytosis: Among the analyzed 628 hospitalizations, only 3 patients were diagnosed with idiopathic thrombocytosis. In all 3 cases the patients were diagnosed with the JAK2 V617F mutation. These incidences of thrombocytosis were classified as moderate (2 cases) and mild (1 case), which did not require treatment; no thromboembolic incidents were found. The frequency of idiopathic thrombocytosis amounted to 3/628 (0.47%) among all the incidents of thrombocytosis and 3/12910 (0.02%) of all hospitalizations.

Procedure: In all the analyzed cases of primary thrombocytosis, no clinical symptoms of disorders of hemostasis were found. No patient, with one exception, experienced thromboembolic complications associated with thrombocytosis. One patient with extreme secondary thrombocytosis (traumatic damage to the spleen requiring splenectomy) was diagnosed with splenic vein thrombosis. The patient required anticoagulation, which was performed using the enoxaparin.

In all cases of secondary thrombocytosis, the platelet number normalized after curing the underlying diseases. There was no indication for prevention using anticoagulants or platelet aggregation inhibitors.

Discussion

The cause of hospitalization in the vast majority of analyzed cases were not incidences of thrombocytosis. This parameter was only examined by us additionally. The authors focused on the etiological factor and age group. Most often, children reported due to infections and these were one-time stays. The course of thrombocytosis was always asymptomatic, although in many cases this phenomenon must be treated as an exponent of the state of acute infectious process, such as ESR, CRP, fibroin or ferritin, and procalcitonin. Some patients were hospitalized several times for various reasons.

Primary thrombocytosis is an extremely rare hematologic disorder in children, which occurs with the frequency of 1:10 million [4], has a much greater number of platelet counts, since in 2/3 patients the platelet number exceeded 1000 G/L and increased proliferation of megakaryocytes in bone marrow. The average age of newly diagnosed thrombocytosis is 11 years [1, 5]. It is a clonal disease derived from a multipotent hematopoietic cell. Expression of the disease manifests itself mainly in the megakaryocytic line, without significant variations in granulocytic and red blood cell systems. Megakaryocytes in patients with thrombocytosis have increased sensitivity to the thrombopoietin stimulation [1, 4. 5]. Important for the course of the disease and the intensity of megakaryopoiesis is the JAK2 V617F mutation in progenitor cells, which is, however, found only in 20% of pediatric patients, compared to 35-60% in adults [4, 6, 7, 8, 9].

The course of disease is slow, with rarely occurring incidents in the form of blood clots and bleedings (affecting 30% of patients) [4]. Bleeding disorder occurs less often than thrombotic complications. The risk of thrombosis (arterial, venous, within the microcirculation) at the time of diagnosis and during the observation period is 7.6 – 29.4%, while bleeding is 3-8.1% [10]. The risk of bleeding increases with the increase of the number of platelets. Particularly high risk of the occurrence of the symptoms of hemorrhagic diathesis occurs when the platelet number exceeds 1500 G/L. Hemorrhagic diathesis in thrombocytosis is a vascular and/or thrombocytopenic hemorrhagic diathesis. In pathogenesis, we should also take account of the so-called Von Willebrand disease [3], in case of which we can observe the reduction in the concentration of large multimers of the von Willebrand factor in blood and increase in small molecule multimers. This results in the reduction of the activity of vWF. The mechanism of this process and its relationship with thrombocytosis, is not fully explained, and it appears that of great importance is degradation and increased consumption of large multimers, due to increased amounts of blood platelets [3]. The risk of thrombotic complications seems to be, however, related more with patient's burdens (age, thrombotic complications in the history, cardiovascular risk factors), than with the very essence of the disease (leukocytosis, JAK2 V617F mutation) [11]. Increased leykocytosis, JAK2 V617F mutation, as well as high content of V617F allele of JAK2 gene are classified as potential factors of thrombotic risk [10, 12]. However, we must discuss the impact of polymorphism of the promoter region of the PAI-1 gene [9]. In the assessment of risk factors for thrombosis, helpful is the IPSET scale (the International Prognostic Score of Thrombosis in WHO-diagnoses Primary Thrombocythemia). It allows to classify the patient to the risk group, and thus to forecast the occurrence of possible thrombotic complications [9, 11].

Among the symptoms occurring at the diagnosis, we should point out the following: splenomegaly (50% of patients), hepatomegaly (25% of patients), paresthesia, ischemia of distal parts of the body and ischemia of the central nervous system [4]. A long-term course of the disease may result in marrow fibrosis in about 20% of patients, and in about 5-10% of cases we can observe the development of acute leukemia, however, one third of patients do not report any symptoms [2]. We should take into consideration that more and more frequent cause of death of the patient with primary thrombocytosis is the development of secondary hematologic or non-hematologic cancer (Hodgin's lymphoma, MALT lymphoma of the stomach, adenocarcinoma), which may be affected by the applied treatment [13]. Differentiation of primary and secondary thrombocytosis in children is shown in Table 4.

Criteria	Idiopathic thrombocytosis	Secondary thrombocytosis
Child's age at diagnosis	In most cases above ten years of age	In most cases under second year of age
Duration of thrombocytosis	Months, years	Days, weeks
Spleen enlargement	Often	Seldom
Systemic Inflammatory Response Syndrome (SIRS)	No	Often
Fever	None	Often
Laboratory abnormalities	Prolonged bleeding time, prolonged PT/PTT in 20% of cases	↑CRP, ↑fibrinogen, ↑WBC, ↓HGB, ↑concentrations of proinflammatory cytokines, ↑VWF
Platelet number	Generally >1000 G/L	Generally <800 G/L
Platelet function	Incorrect	Correct
Platelet morphology	Large or small dysmorphic: huge platelets, with insets, non-granular, platelet conglomerates, fragments of megakaryocytes	Large with normal morphology

Table 4: *Differential diagnosis between primary and secondary thrombocytosis in children (acc. to [7])*

The treatment of primary thrombocytosis, in case of which we do not observe neither thrombotic incidents, nor hemorrhagic diathesis, and the platelet number that does not exceed 1500 G/L, is not recommended [1]. In patients with a high risk of bleeding complications, a good result can be obtained through the treatment with hydroxyurea. Long-term use of this medication in children, however, arouses great controversy, due to the suspected increase in the risk of developing the cancer [8, 14]. An alternative to hydroxycarbamide is anagrelide, which by affecting the maturation of megakaryocytes, reduces the level of platelets and does not stimulate the process of carcinogenesis [3]. In the treatment of recurring thrombosis, it is also worth to apply a low-dose acetylsalicylic acid (ASA), which reduces the platelet aggregation [1]. However, the use of aspirin in children under 12 years of age requires great caution, due to the risk of the development of the Reye's syndrome [11, 14]. Implementation of the treatment of primary severe thrombocytosis always requires caution, due to the potential risk of complications, such as myelosuppression or blastic transformation.

Secondary thrombocytosis is a relatively common hematological disorder, observed in hospitalized children. Mild thrombocytosis is observed in 72-86% cases, moderate and severe thrombocytosis is observed in 6-8% cases, while extreme thrombocytosis is observed in 0.5-3% cases [5, 15]. The most common causes leading to secondary thrombocytosis in children, are infections of bacterial and viral etiology, both in acute and chronic course [16]. Often observed cause is anemia, due to iron deficiency (i.e. iron-deficiency anemia), in the case of which the observed thrombocytosis is associated probably with increased levels of anemia-induced erythropoietin [17]. However, the pathological mechanism of secondary thrombocytosis in patients with IDA has not been fully developed yet [18]. Among examined children, a large group is represented by patients with cancer: thrombocytosis is most often observed in liver embryonic cancer (excessive production of thrombopoietin in the malignant tumor of the liver), embryonic neuroma, as well as in lymphomas and leukemias before cytoreduction (especially chronic myelogenous leukemia, which, like idiopathic thrombocythosis, belongs to the same group of diseases – chronic myelodysplastic syndromes) [15]. An increased platelet number, persisting for weeks, months, and even years after the surgery, is also observed after splenectomy (injuries, spherocytosis). Incidents of reactive thrombocytosis after splenectomy are estimated at 75%-82% [19].

Thrombocytosis may also be induced iatrogenically. Medications that induce the increase in platelets are: adrenaline, which causes injection of the pool of platelets accumulated in the spleen to the bloodstream, as well as cyclosporine, corticosteroids, especially in children in the course of cancer treatment (acute leukemias, lymphomas), and antibiotics, such as: meropenem and imipenem [15].

The pathogenesis of secondary thrombocytosis has not been completely developed yet. Worth noting is the role of cytokines (interculines, such as IL-3, IL-6 and IL-11) and thrombopoietin, which stimulate megakaryopoiesis, resulting in the increase in the number of platelets [18]. In inflammation processes, the production of IL-6 in macrophage fibroblasts increases, together with a simultaneously-observed increase in the concentration of the granulocyte growth factor GM-CSF [1, 16, 20]. Inflammatory factors also lead to the reduction in the level of hemoglobin, by disturbed erythrocyte production (due to disturbances in iron management and inhibition in suppression of erythropoietin), or shortening their life. There is a direct relationship between the number of platelets and the value of white blood cells, as well as an inversely-proportional relationship between the intensity of thrombocytosis and the seriousness of anemia [16, 21].

The occurrence of secondary thrombocytosis in our analysis also showed the dependence of age. The diagnosis was made mostly in children under 2 years of age. Similar results were obtained in research conducted by Őzcan et al. [21], which showed that the incidence of secondary thrombocytosis was most common in the period between twelve and twenty-four months of age. In the cited study, the most common cause of reactive thrombocytosis in this age group were infections.

The frequency of the occurrence of reactive thrombocytosis associated with infections, is specified in the literature in the range of 37-78%, wherein the respiratory tract infections account for 60-80% of cases (21). In our study, respiratory tract infections amount to 40%. In addition, each of the analyzed age group was dominated by mild thrombocytosis.

The course of secondary thrombocytosis is usually asymptomatic, and the platelet number is normalized after curing the underlying disease [22].

There is no indication to conduct prophylaxis with anticoagulants or platelet aggregation inhibitors, even if the platelet level > 1000 G/L, unless there coexist risk factors for thrombotic complications [15].

Conclusions

1. Thrombocytosis in children is observed in 4.86% of hospitalizations in the department of pediatrics, hematology and oncology. The most common cause of thrombocytosis are infections and anemia due to iron deficiency.
2. The occurrence of thrombocytosis shows the dependence of age. The diagnosis is most often made in children under 2 years of age.
3. In each of the analyzed group was demonstrated the highest incidence of mild thrombocytosis.
4. Idiopathic thrombocytosis is a very rare disease in children and represents 0.47% of all incidents of thrombocytosis.
5. The course of secondary thrombocytosis is usually asymptomatic, and the platelet number is normalized after curing the underlying disease.
6. In secondary thrombocytosis it is not indicated to conduct routine prophylaxis with anticoagulants or platelet aggregation inhibitors.

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