Thrombocytosis in Childhood

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ABSTRACT

Thrombocytosis is a frequent finding in hemograms obtained from hospitalized and ambulatory children due to the widespread use of automated blood cell counters. Pediatricians are commonly puzzled in cases of thrombocytosis to determine the underlying cause and the need for therapy. The purpose of this review is to assist the general pediatrician into dealing with this common hematological finding in every day clinical practice. Fortunately, primary thrombocytosis or essential thrombocythemia, a clonal disease, is exceedingly rare in childhood, but may be associated with thromboembolic and hemorrhagic complications. On the other hand, secondary or reactive thrombocytosis is very common and is due to a variety of conditions, such as acute and chronic infections, iron deficiency, bleeding, hemolytic anemias, collagen vascular diseases, malignancies, drugs and splenectomy. Treatment of reactive thrombocytosis should be directed to the underlying problem alone. Administration of platelet aggregation inhibitors such as aspirin is unwarranted. Consultation is necessary only for the rare child with extreme thrombocytosis who has clinical and/or laboratory criteria consistent with essential thrombocythemia, or in whom a hemorrhagic or thrombotic complication has developed.

Key words: *Children, Essential thrombocythemia, Reactive thrombocytosis, Thrombocytosis, Thrombopoietin.*

Thrombocytosis (TS) or elevation in the peripheral blood platelet count to values >400,000/μL is common in infancy and childhood, occurring in 3 to 13% of children(1). Extreme thrombocytosis (platelets >1,000,000/μL) is uncommon, occurring in less than 2% of children(2), but may be more common in critically ill children(3). While in older adults an elevated platelet count can signify an underlying hematological disease, in children in almost every case the elevated platelet count is due to another medical condition, such as acute infection, chronic inflammation, collagen vascular and renal diseases, Langerhan's cell histiocytosis, iron deficiency, hemolytic anemia, and Kawasaki disease (KD)(4-18). Drugs are another less frequent cause of secondary thrombocytosis in children(19-30). Splenectomy is a surgical cause of thrombocytosis that can occasionally be extreme, but without physiological consequences, unless associated with thrombophilic factors.

Much rarer in childhood is primary thrombocytosis, which is divided into familial and essential. The first has been described in a number of families and appears to be heterogeneous as to the underlying pathophysiological mechanism(31-37), while essential thrombocytosis, also known as essential thrombocythemia (ET), is a chronic clonal myeloproliferative disease(38-45). The purpose of the present review is to discuss the physiology of megakaryopoiesis and the causes and management of TS in children.

PHYSIOLOGY OF THROMBOPOIESIS

Thrombopoietin (Tpo) is the key regulator of platelet production in humans, and is primarily expressed in the liver, and to a lesser extend the kidneys, bone marrow and other organs(46). It acts on the commitment of hematopoietic stem and progenitor cells into platelet-specific differentiation through its c-mpl receptor that is also expressed on pluripotent megakaryocytes, platelets, and endothelial cells. C-mpl receptors normally remove circulating Tpo by cellular absorption and internalization. Hepatic Tpo expression is unchanged in the presence of thrombocytopenia. Tpo serum concentrations are normal if thrombocytopenia results from platelet destruction, while are elevated if thrombopoiesis drops. Longitudinal Tpo measurements in infants and children with acute infections, surgical trauma and other conditions show that the elevation of circulating Tpo concentration precedes TS (18,47-49). Tpo serum levels are significantly higher in patients with ET than in patients with reactive TS, although Tpo serum levels are not correlated with platelet counts in patients with ET(50).

Besides Tpo, other cytokines or hematopoietic growth factors, such as stem cell factor, granulocyte-macrophage colony stimulating factor, IL-6, IL-8 and IL-11 play a major role in certain steps of megakaryopoiesis and thrombopoiesis(51,52).

PLATELET COUNTING

A gold standard method for platelet counting has not been clearly defined. One study compared impedance, optical density, and CD61 immuno-staining for platelet counting with the reference method of flow cytometry in children. Samples were analysed and divided into specific age-related groups and groups with thrombocytopenia and thrombocytosis. Data analysis showed that the CD61 method compared best with the reference method in all specified groups, although the impedance count method was also accurate despite its limitations, since abnormally small or fragmented red cells can be falsely counted as platelets with impedance-based automated counters(53). In these cases examination of a well-stained peripheral blood smear is invaluable in documenting thrombocytosis, and in assessing the size and granulation of the platelets and the size of the red blood cells.

In many children with secondary thrombocytosis, the underlying disease is clinically apparent. However, it is not uncommon to diagnose thrombocytosis in asymptomatic children undergoing hemograms as part of routine blood work. Although in the vast majority of these cases thrombocytosis is mild and transient and results from a recent infection that has already subsided by the time of phlebotomy, in rare individual cases it may be very hard to differentiate between essential and reactive thrombocytosis. The distinction between clonal (essential) and reactive thrombocytosis is clinically relevant because the first is associated with thromboembolic and hemorrhagic complications, while the latter is not.

REACTIVE THROMBOCYTOSIS

Secondary or reactive thrombocytosis in childhood results from increased thrombopoiesis, as a reactive process due to an underlying infection, chronic inflammation, injury, malignancy, and surgical or functional splenectomy. Causes of reactive thrombocytosis are listed in ***Table* I**. From various published

TABLE I CAUSES OF SECONDARY OR REACTIVE THROMBOCYTOSIS IN CHILDREN

Infections (*e.g.*, of the respiratory tract, gastrointestinal tract, central nervous system, skeleton and others)
Iron deficiency anemia, hemolytic anemias
Bleeding
Connective tissue diseases (juvenile rheumatoid arthritis, small and large vessel vasculitides including Wegener's granulomatosis, polyarteritis nodosa and others)
Kawasaki's disease
Inflammatory bowel diseases
Langerhans cell histiocytosis
Malignancies (mostly solid tumors, such as hepatoblastoma, hepatocellular carcinoma, neuroblastoma, rarely acute lymphoblastic leukemia)
Drugs (adrenaline, corticosteroids, vinca alkaloids, iron, miconazole, antibiotics, haloperidol, narcotics, non-narcotic psychopharmaceutical agents)
Trauma, burns, tissue injury
Intense exercise
Splenectomy (surgical or functional *e.g.*, sickle cell anemia)

series, it seems to affect up to 15% of hospitalized children(1-6). It is more common in neonates, particularly premature ones, and infants up to 2 years of age and less common in older children. In most children with reactive thrombocytosis, platelet counts are modestly elevated up to 700,000/μL. Moderate thrombocytosis (platelets between 700,000 and 1,000,000/μL) occur in 6-8% of children with reactive thrombocytosis, while platelets >1,000,000/μL occur in less than 2-3% of children with reactive TS(4).

Infections, both viral and bacterial, are by far the most common cause of secondary thrombocytosis in childhood. Presently, infections of the respiratory tract account for 60-80% of cases of secondary thrombocytosis in children(2,4,5,7-10,12), followed by infections of the urinary(11) and gastrointestinal tracts, and of the bones(4,5,12,54). This was not the case before the 1980s, when infections of the central nervous system, particularly bacterial meningitis due to *Hemophilus infuenzae* was one of the most common causes of reactive thrombocytosis(12-14). ***Table* II** shows the etiologic factors of thrombocytosis in various pediatric series(2,5,6,12).

One study assessed the development of reactive thrombocytosis in 311 children with cerebrospinal fluid culture-positive bacterial meningitis. thrombocytosis was seen in 49% of the patients after the first week of treatment. Platelet counts were higher in infants and in patients with long duration of illness prior to admission. Subdural effusion and antibiotic therapy were associated with more pronounced thrombocytosis(14).

Regarding infections of the respiratory tract, thrombocytosis is a common finding among patients with lower respiratory tract infections, being particularly prominent in those with pleural effusions or empyema(2,4-10,12). Lobar pneumonia without effusion can also be associated with thrombocytosis, but typically of a lesser magnitude compared to pneumonia with effusion. In one study, thrombocytosis occurred in about 40% of children with lower respiratory tract infections due to *Mycoplasma pneumoniae*(9). Thrombocytotic patients with pneumonia may have a more severe clinical course, although this is questionable(7).

Reactive thrombocytosis is also common in urinary tract infections. The relationship between reactive thrombocytosis and the site of urinary tract infection was studied in 48 children. Platelets were counted before, during, and after treatment. Reactive thrombocytosis was noticed in 74% of children with upper versus 14% with lower urinary tract infections(11). Hence, reactive thrombocytosis is much more common in urinary tract infections with renal parenchymal involvement during the recovery phase.

TABLE II ETIOLOGIC FACTORS OF THROMBOCYTOSIS* IN VARIOUS PEDIATRIC SERIES

Study	N	Infections	Hemolytic anemia or other hematological cause	Tissue damage (*e.g*., surgery)	Malignancy or post-chemotherapy	Other etiological factors
Yohannan,†*et al.*(2)	663	203(30.6%)	128(19.3%)	101(15.2%)	13(2%)	76(11.5%)
Heng,††*et al.*(5)	135	105(78%)	4(3%)		7(5.2%)	–
Vora, *et al.*(6)	36	27(75%)	–	2(5.5%)	6(16.7%)	–
Chan,**_et al._.(12)	100	37(37%)	22(22%)	21(21%)	–	10(10%)

 # Definition of thrombocytosis: Yohannan, *et al., >500,000 / μL;* Heng, *et al., >600,000/ μL; Vora, et al., > 800,000/ μL; Chan, et al.*, >900,000/ *μL;*

* *Including iron deficiency anemia, recovering ITP, etc.*

†*In 98 (14.8%) additional cases the authors considered thrombocytosis to be a rebound phenomenon.*

†† *9 (6.7%) cases were due to Kawasaki's disease.*

** *94 patients with 100 episodes of thrombocytosis.*

From the non-infectious causes of secondary thrombocytosis, iron deficiency is a common one, since it is the single most common nutritional deficiency worldwide(16,17). The fact that thrombocytosis is more frequent in children up to 2 years of age is partly due to the higher incidence of iron deficiency in this age group. Hemolytic anemias are another frequent cause of thrombocytosis. Sickle cell anemia is a congenital hemolytic anemia associated with thrombocytosis due to increased bone marrow platelet production, but also due to functional asplenia from the repetitive splenic autoinfarcts. Patients with sickle cell anemia and thrombocytosis are at increased risk for vasocclusive complications, such as brain infarcts, painful crises, while they have highly impaired full scale IQ(55,56). Finally, splenectomized patients are expected to have high postoperative platelet counts because of reduced platelet storage in the spleen.

Autoimmune diseases, such as juvenile rheumatoid arthritis (JRA)(57), small and large vessel vasculitides including polyarteritis nodosa(58), and Wegener's granulomatosis(59), KD(16), Henoch-Schoenlein purpura(60), and inflammatory bowel diseases(61) account for <10% of cases of reactive thrombocytosis in children. In patients with systemic-onset JRA, serum IL-6 levels correlate with platelet counts and with the extent and severity of joint involvement(57). Regarding KD, thrombocytosis typically occurs in the second week of the illness, and it is therefore not helpful in making a timely diagnosis. Moreover, the absence of thrombocytosis during convalescence does not exclude the disease. Tpo in conjunction with IL-6 contributes to the thrombocytosis of patients with KD. Tpo serum levels are also increased in patients with inflammatory bowel diseases, irrespective of disease activity, platelet counts and clinical characteristics of the patients(62).

Langerhans cell histiocytosis (LCH), a disease with unpredictable clinical reactivations is also associated with thrombocytosis and platelet count is an indicator of disease activity in LCH(63).

Malignancies, particularly solid tumors of the liver, such as hepatoblastoma and hepatocellular carcinoma are uncommon causes of reactive thrombocytosis in childhood(64-68). The association between liver tumors and thrombocytosis is likely due to the increased production of hepatic Tpo in these patients. Reactive thrombocytosis has also been described in children with other small, blue round cell tumors of childhood, such as neuroblastoma(68). Interestingly, Blatt, *et al*. (69) described 7 children, all boys, out of 217 (3.2%) with acute lymphoblastic leukemia who had platelet counts greater than 400,000/μL at diagnosis of the leukemia. Other than male sex, no clinical or laboratory characteristics were clearly associated with TS in these children.

Reactive thrombocytosis can also be related to treatment with several drugs(19-30). Adrenaline and corticosteroids are known to cause transient thrombocytosis, as a result of release of stored platelets from the spleen into the blood circulation(60). Various antibiotics such as carbapenems and cephalosporins are also claimed to cause thrombocytosis in children(20-22,25-29). However, it should be noted that several of the reports describing the development of thrombocytosis after antibiotics are from the 1970s and 1980s, *i.e.*, before the role of Tpo and the kinetics of platelet production had been clarified. The more recent analysis of serum Tpo concentrations helped to clarify the role of Tpo in reactive thrombocytosis. In the first week, when platelet counts are normal, circulating Tpo concentrations rise and then gradually decrease. When platelet counts peak during convalescence, Tpo concentrations are back to normal. Hence, the development of thrombocytosis during the recovery phase after appropriate antibiotic therapy for an infection is consistent with the bone marrow response to Tpo and not the result of the antibiotic(29,47). Unless re-challenge with the same antibiotic under baseline conditions results in thrombocytosis, the association between the antibiotic and thrombocytosis should be considered unproven. Among other drugs, vinca alkaloids have been convincingly shown to induce thrombocytosis(19). Miconazole has also been implicated in causing thrombocytosis, as documented by drug re-challenge. The simultaneous administration of ciprofloxacin and tazobactam/piperacillin caused thrombocytosis in a single

patient, since the platelet count started to increase immediately after initiation and dropped immediately after discontinuation of the drug(25). Late-onset transient thrombocytosis has been described after acute accidental overdosage with haloperidol(70). Neonatal reactive thrombocytosis has been described from maternal narcotic drug abuse(71), but may also occur in infants born to mothers treated during pregnancy with non-narcotic psychopharmaceutical agents(30). Finally, reactive thrombocytosis may be due to multiple, simultaneous, causative factors. In one pediatric series, 9% of cases of secondary thrombocytosis were multi-factorial(72).

Reactive thrombocytosis in children does not require treatment with platelet aggregation inhibitors, such as aspirin, even if the platelet count is greater than 1,000,000/μL, unless additional well-defined thrombophilic risk factors exist. Hence, treatment should be directed to the underlying disease and not to the platelet count.

ESSENTIAL THROMBOCYTHEMIA

ET is a diagnosis of exclusion. In order to make the correct diagnosis, the diagnostic criteria proposed by the Polycythemia Vera Group are applied (***Table* III**)(73). The Italian Society of Hematology has published recommendations on when to start platelet-lowering therapy, and with what agent in patients with ET in order to prevent thrombotic complications(74).

TABLE III DIAGNOSTIC CRITERIA OF ESSENTIAL THROMBOCYTHEMIA

1. Platelet count >600,000/μL
2. No known causes of reactive thrombocytosis absence of fever, normal erythrocyte sedimentation rate, normal or elevated leukocyte alkaline phosphatase.
3. An increase in and clustering in the bone marrow of abundant mature giant megakaryocytes with hyperploid nuclei, normal or slightly increased bone marrow cellularity, absent bone marrow collagen fibrosis or fibrosis in <1/3 of the biopsy area.
4. Spontaneous megakaryocyte colony formation in bone marrow progenitor assays.
5. No preceding or associated other myeloproliferative disorder or myelodysplastic syndrome (no bcr/abl gene rearrangement, no cytogenetic or morphologic evidence for a myelodysplastic syndrome, hematocrit <46% or normal red blood cell mass).
6. Splenomegaly detected on physical examination and/or by imaging studies.

ET is extremely rare in childhood with an incidence of 1 per million children, *i.e*., 60 times lower than in adults(38-45). Despite that, it should be clarified that reactive or secondary thrombocytosis is more common than ET in all age groups except those >80 years old, because the mechanisms responsible for secondary thrombocytosis are operational in adults as well. Forty-eight children with ET were described in the medical literature prior to 2006, with the age ranging from 6 weeks to 18 years (median 11 years). The platelet count is usually >1,000,000/μL, while platelet function is typically abnormal. Morphological abnormalities of platelets in ET include bizarre forms, giant platelets, platelet conglomerates, circulating megakaryocytic fragments, and hypogranularity. The disease is due to a clonal defect in hematopoietic or megakaryopoietic progenitors that typically display decreased c-mpl expression. About 30% of children experience thromboembolic or hemorrhagic complications at the time of diagnosis or during the course of the illness and 15% will eventually die because of the underlying disease or from development of leukemia or myelofibrosis. Hence, ET like polycythemia vera is a pre-malignant condition. Indications for treatment are not well established in asymptomatic patients, but patients with thromboembolic or hemorrhagic complications and those with extreme thrombocytosis (> 2,000,000/μL) and prolonged bleeding times may deserve treatment. Dror, *et al*.(45) from the Hospital for Sick Children in Toronto reviewed the clinical course of 36 children with ET, of whom only 15 had symptoms directly related to their hematological problem, including 9 who had severe thromboembolic and hemorrhagic complications. Symptomatic patients had significantly higher platelet counts (2,419,000/μL versus 904,000/μL, P<0.001). However, 3 patients with platelets <800,000/μL had thrombotic events. Moreover, 3 patients who had thrombotic events and did not receive therapy went on to have a benign clinical course(45). From these data, it is evident that it is

KEY MESSAGES

- Thrombocytosis is a frequent finding in children due to the widespread use of automated blood cell counters.
- The elevated platelet count in majority of children is a benign, reactive phenomenon due to another underlying medical condition.
- Primary or essential thrombocytosis (thrombocythemia), which is a true myeloproliferative disorder, is extremely rare in children with an incidence of 1 per million children, and is a diagnosis of exclusion.

almost impossible to give evidence based guidelines for therapy in children with ET due to the rarity of this condition and its heterogeneous clinical course.

PRIMARY FAMILIAL THROMBOCYTOSIS

Few familial recessive, dominant, as well as X-linked forms of primary thrombocytosis have been reported(31-37). Spontaneous formation of mega-karyopoietic progenitors and increased sensitivity to Tpo are thought to be the primary mechanisms. In several pedigrees, overproduction of Tpo has been shown to be responsible for the disease. In some adult patients mutations in the Tpo gene locus have been found. These mutations typically occur in the 5' untranslated region of the Tpo gene and result in deletions of untranslated open reading frames and overproduction of Tpo. In children with familial thrombocytosis, platelet counts are lower than in ET, splenomegaly is usually absent, almost no thrombotic or hemorrhagic complications occur, and treatment is not typically required.

In conclusion, thrombocytosis even when marked, is typically a benign, reactive phenomenon in children that does not require treatment. Although it is more common in hospitalized children who suffer from a variety of underlying conditions, it can also be seen in normal children during routine blood work, usually as a result of a recent self-limited infection. A repeat hemogram in a few weeks, provided that the child remains well, will show normalization or at least a substantial drop in the platelet count. In most cases, consultation with a pediatric hematologist is not required unless the primary physician and/or the parents are anxious and in cases that thrombocytosis is unexplained, prolonged, or symptomatic, *i.e.*, it is associated with thrombotic and/or hemorrhagic complications. In these cases, ET can not be excluded, and timely consultation is necessary.

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