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Thrombocytosis in Children: A Recent Perspective

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Abstract

Thrombocytosis is a common condition in children, including primary and secondary types. Secondary thrombocytosis is often caused by infections, anemia, iron deficiency, trauma, or surgery, generally without serious thrombosis or bleeding. Platelet counts usually return to normal after controlling the primary factors, with a good clinical course and outcomes. Primary thrombocytosis is mainly caused by myeloproliferative neoplasms such as polycythemia vera, primary thrombocythemia, and myelofibrosis, often accompanied by hematopoietic cell gene mutations. Clinical manifestations are atypical compared to adults, with few thromboembolic or bleeding events. Patients who are asymptomatic or have mild symptoms generally do not require special treatment, and it is recommended to monitor platelet values regularly. Antiplatelet therapy with aspirin can be considered for patients at risk of thrombosis or those with extreme thrombocytosis. Cytoreductive therapy can be performed when necessary, but it is important to monitor drug toxicities and side effects closely. Currently, commonly used cytoreductive drugs include hydroxyurea, interferon-alpha, and anagrelide. This article provides an overview of the etiology, clinical manifestations, diagnosis, and treatment of childhood thrombocytosis, aiming to further guide clinicians in treatment decisions.

Keywords: Thrombocytosis; Thrombocythemia; Child

Introduction

Platelets are produced by bone marrow megakaryocytes and exist in blood circulation as non-nucleated, disc-shaped cells, playing an important role in regulating hemostasis and coagulation [1]. Megakaryocytes are regulated by various growth factors and cytokines, among which thrombopoietin plays a crucial role. Thrombopoietin is primarily synthesized by the liver, with small amounts also produced by bone marrow stromal cells, kidneys, and the spleen. It binds to the thrombopoietin receptor and activates relevant signaling pathways, thereby regulating stem cell

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differentiation and megakaryocyte maturation [2]. During inflammatory states, liver synthesis of thrombopoietin increases, with interleukin-6 and interleukin-11 participating in its regulatory process [1, 2].
A platelet count ≥450 ×109/L in children defines thrombocytosis, classified based on platelet count into mild (450 × 109/L ~ <700 × 109/L), moderate (700 × 09/L ~ <900 × 109/L), severe (900 × 09/L ~ <1,000 × 109/L), and extremely severe (≥1,000×109/L) [3]. The incidence of primary thrombocythemia in children is lower than in adults. Studies show that primary thrombocythemia occurs in children under 16 years old at a rate of 0.004/100,000 to 0.11/100,000, while the adult incidence rate is 1.03/100,000, and in children and young people under 20 years old, it is 0.6/100,000 [1, 3].

Etiology and Pathogenesis

The causes of thrombocytosis in children include primary and secondary categories. Secondary thrombocytosis, also known as reactive thrombocytosis, is mainly caused by external factors stimulating megakaryocyte production, typically presenting as transient or temporary thrombocytosis. Common causes of secondary thrombocytosis include infection, inflammatory diseases, iron deficiency, anemia or bleeding, post-splenectomy or splenic dysfunction, medications, trauma or surgery, and malignant tumors. These factors increase the production of numerous inflammatory compounds (such as interleukin-6), significantly increasing thrombopoietin secretion and megakaryocyte production [4, 5]. Bacterial and viral infections are common causes of thrombocytosis in children [1]. The exact mechanism by which iron deficiency causes secondary thrombocytosis remains unclear. However, it may be related to the increased proliferation of common progenitor cells of platelets and red blood cells and increased megakaryocyte production, ultimately resulting in increased circulating platelets. Thrombocytosis is more common in neonates and young children than in older children and more prevalent in preterm infants than in full-term infants. Neonatal thrombopoietin concentrations are higher than in adults and increase after birth. Most thrombocytosis at this time is secondary, spontaneously regressing, and rarely resulting in bleeding or thromboembolic complications [4].

Primary thrombocythemia is caused by intrinsic defects in megakaryocytes or their precursor cells, leading to dysregulation of platelet production characterized by clonal expansion of hematopoietic cells. Generally, genetic mutations associated with hematopoiesis can be detected. Somatic driver variations in genes regulating platelet production result in clonal hyperplasia of the bone marrow, particularly involving the JAK2, CALR, and MPL genes, which are closely associated with myeloproliferative neoplasms [5]. Myeloproliferative neoplasms mainly include Philadelphia chromosome-positive tumors like chronic myeloid leukemia and Philadelphia chromosome-negative tumors such as polycythemia vera, primary thrombocythemia, and primary myelofibrosis (PMF) [6]. JAK2 and MPL mutations activate the JAK-STAT signaling pathway, leading to cytokine-independent clonal myeloproliferation. The exact mechanism by which CALR mutations induce bone marrow proliferation is unclear. However, it may be related to mutant CALR binding to the extracellular domain of MPL in the endoplasmic reticulum, causing dimerization and translocation to the cell surface, activating the JAK-STAT signaling pathway [5]. Over half of primary thrombocythemia cases express JAK2, CALR, or MPL mutations, which are usually mutually exclusive. Other clonal mutations may also exist, complicating the clinical phenotype through impacts on epigenetic regulation (e.g., ASXL1 and TET2), RNA splicing (e.g., SRSF2, SF3B1), and transcriptional regulation (e.g., TP53, IKZF1), promoting disease progression and leukemic transformation [6, 8]. Familial thrombocytosis is extremely rare, often caused by germline mutations in genes encoding thrombopoietin, thrombopoietin receptors, and receptor effector protein kinases, including various mutations in the thrombopoietin, MPL, and JAK2 genes. It is generally manifested by thrombocytosis and splenomegaly without abnormal white or red blood cells, with potential risks of thrombosis, bleeding, and possible transformation into leukemia or myelofibrosis [7].

Clinical Manifestations

Clinical manifestations of secondary thrombocytosis primarily reflect underlying diseases. Myeloproliferative neoplasms are mainly characterized by the amplification of terminal myeloid cells in peripheral blood, leading to increased red blood cells, white blood cells, platelets, bone marrow fibrosis, and splenomegaly, and are prone to clonal evolution and disease transformation. Gene mutations, thrombotic or bleeding events, and disease progression rates commonly seen in adult patients are relatively uncommon in children [9, 10]. A systematic review including 396

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primary thrombocythemia and 75 polycythemia vera pediatric patients found that the thrombosis rate in polycythemia vera patients was about 9.3%, and in primary thrombocythemia patients, it was about 3.8%. Bleeding complications were rare, with a pre-diagnosis bleeding complication rate of about 1% in primary thrombocythemia patients and about 4.8% post-diagnosis. The bleeding occurrence rate before and after diagnosis was approximately 4% in polycythemia vera patients [8].

Pediatric primary thrombocythemia is rare, with studies finding an annual incidence of approximately 1 per 10 million in children aged 14 and below, equivalent to 1/60 of the adult rate. Thrombocytosis is the main hematological feature of primary thrombocythemia and the most common myeloproliferative neoplasm in children [9]. Common clinical manifestations of primary thrombocythemia include vasomotor symptoms (such as headaches, syncope, acral paresthesia, erythromelalgia, and visual disturbances), thrombosis, bleeding, and splenomegaly. Fifty percent of children present without symptoms, and headache, bone pain, and splenomegaly are the most common symptoms in children [10].

Diagnosis

A platelet count ≥450 × 109/L in the peripheral blood cells of a child can diagnose thrombocytosis. A recent history of infection, trauma, surgery, previous splenectomy, significant bleeding, or iron deficiency mainly suggests secondary thrombocytosis. Unexplained fever, weight loss, fatigue, or other systemic discomfort suggests malignancy. Previous arterial or venous thrombosis suggests myeloproliferative neoplasms [1]. Laboratory tests must first exclude secondary thrombocytosis causes, including inflammatory markers and serum ferritin. When primary thrombocythemia is suspected, JAK2, MPL, and CALR mutations should be analyzed. If necessary, methods such as next-generation genomic sequencing, single-cell genomics, and whole-genome sequencing should be used to detect relevant clonal mutations. Molecular and/or cytogenetic analysis can help distinguish primary thrombocythemia from other myeloproliferative disorders and provide prognostic information on primary thrombocythemia [10].

Detection of JAK2 V617F, CALR exon nine mutations, and MPL exon 10 mutations can identify more than 75% of adults with primary thrombocythemia. However, the absence of these mutations does not rule out the diagnosis of primary thrombocythemia, as up to 20% of cases may be triple-negative, and most pediatric patients with primary thrombocythemia lack these clonal markers. This further indicates that diagnostic criteria for adult primary thrombocythemia may not be suitable for children, necessitating broader mutation testing for validation [13-14]. The WHO proposes that diagnosing adult primary thrombocythemia requires meeting four major criteria or the first three major criteria plus minor criteria [11]. The major criteria include: [1] platelet count ≥450×109/L; [2] bone marrow biopsy showing megakaryocyte hyperplasia, with increased mature megakaryocytes having highly lobulated nuclei, no significant increase in granulocyte or erythrocyte production or left shift, and rarely mild increase in reticular fibers (grade 1); [3] exclusion of chronic myeloid leukemia, polycythemia vera, PMF, or other myeloid neoplasms; [12] presence of JAK2, CALR, or MPL gene mutations. Minor criteria include the existence of other clonal markers (ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, or SF3B1 mutations) and excluding secondary thrombocytosis.

Treatment

Without other risk factors, secondary thrombocytosis in healthy children does not require specific treatment; only treatment for the underlying disease is needed. As the cause is treated, platelets usually return to normal. No targeted management is required if the platelet count is not significantly elevated. US and European guidelines recommend dynamic observation of platelet count for six months [10, 13]. There is limited research on how much adult recommendations apply to children and how to treat children with primary thrombocythemia. The thromboembolic formation is one of the serious complications of thrombocytosis.

Since the occurrence of thromboembolic events is age-related, the incidence of thromboembolic complications in children with primary thrombocythemia may be lower. Some studies have found that JAK2 V617F-positive primary thrombocythemia in children results in more frequent thrombosis than in adults [13]. It should be noted that reported thrombotic events in children often present with severe clinical manifestations. One report of 89 children with

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thrombocythemia included three cases complicated by Budd-Chiari syndrome and one case with cerebral venous thrombosis [14].

The treatment goal for primary thrombocythemia is to prevent thrombotic and bleeding events and alleviate related symptoms. Currently, there is no cure for this disease, nor can treatment extend survival or prevent disease transformation into acute leukemia or myelofibrosis. There are currently no relevant guidelines or expert consensus recommendations regarding the treatment of children with primary thrombocythemia. Treatment mainly follows individualized treatment plans for adults with primary thrombocythemia. Adult patients are currently stratified for treatment based on the revised International Prognostic Score for Thrombosis in primary thrombocythemia (IPSET-thrombosis) [15]. High-risk (any age with a history of thrombosis; age >60 years and JAK2 V617F mutation positive; meeting either criterion is high-risk) and intermediate-risk (age >60 years and JAK2 V617F mutation negative, no history of thrombosis) patients are recommended to use cytoreductive treatment combined with systemic anticoagulation and/or antiplatelet therapy. Low-risk (age ≤60 years and JAK2 V617F mutation-positive, no history of thrombosis) and very low-risk (age ≤60 years and JAK2 V617F mutation negative, no history of thrombosis) patients are recommended to use antiplatelet monotherapy or dynamic observation [16]. The European LeukemiaNet recommends cytoreductive treatment for platelet counts exceeding 1,500×109/L or in cases of major bleeding episodes. Additionally, cytoreductive treatment may be considered to control systemic symptoms or symptoms related to bone marrow hyperplasia [16]. Due to potential adverse reactions, cytoreductive treatment is generally not recommended for pediatric thrombocytosis. Children with thrombosis, severe bleeding, critical conditions, or unresponsive to initial treatment may consider using cytoreductive treatment [16]. The optimal platelet count target value for low-risk patients is unclear. The platelet count target value should be reduced within the normal range for patients with high-risk factors.

Aspirin is a commonly used antiplatelet drug, recommended at a low dose of 2-3 mg/kg/ day, administered once daily or divided into two doses. It can alleviate microvascular symptoms such as headache or erythromyalgia [16]. Hydroxyurea is a non-specific bone marrow suppressant that can reduce platelet and white blood cell counts, reducing thrombosis and alleviating bone marrow fibrosis. It is a first-line treatment for primary thrombocythemia [17]. Its mechanism of action involves blocking cell proliferation during interphase by inhibiting ribonucleotide diphosphate reductase activity, leading to cell death. Due to its potential leukemogenicity, its use in pediatric patients has been controversial. Recent long-term treatment results in children with sickle cell disease have shown that hydroxyurea has acceptable safety in pediatric patients [20, 21]. Interferon alpha is glycoproteins inhibiting human megakaryocyte precursor cell proliferation, possessing immunomodulatory, anti-proliferative, and anti-angiogenic properties. They inhibit megakaryocyte production by suppressing the expression of cytokines such as granulocyte-macrophage colony-stimulating factor, granulocyte colony-stimulating factor, and interleukins that stimulate platelet production. Interferons can control polycythemia and thrombocytosis, inhibit bone marrow fibrosis, and alleviate splenomegaly, making them effective for patients with polycythemia vera and primary thrombocythemia. Interferon alpha or pegylated interferon alpha is relatively safe for treating younger patients and pregnant women. It thus can be used as a first-line treatment for pediatrics with primary thrombocythemia [2].

Anagrelide can prevent thrombosis in adult patients with primary thrombocythemia, but experience with its use in children is limited. It can be used as a second-line drug for patients unresponsive or intolerant to hydroxyurea or interferon. JAK2 inhibitors were previously mainly used to treat PMF and are now used to treat polycythemia vera patients intolerant to hydroxyurea. A randomized study on ET treatment found that the hematological response rate of the JAK2 inhibitor ruxolitinib was similar to that of first-line therapies, with comparable overall response duration. Its safety and tolerability were similar to reports for polycythemia vera and PMF, making it a treatment option for patients with refractory symptoms [18]. In children, JAK2 inhibitors are mainly used to treat graft-versus-host disease after transplantation, with minimal experience in primary thrombocythemia. Few new drugs are available for treating primary thrombocythemia, with research on lysine-specific demethylase-1 inhibitors and CALR monoclonal antibodies currently in clinical trials, potentially extending to pediatric patients [19].

The currently suggested thresholds and treatment strategies must be validated by prospective data specifically obtained in pediatric primary thrombocythemia. Given the extremely low incidence of pediatric primary thrombocythemia and the need for long-term follow-up, obtaining prospective clinical data is challenging. For asymptomatic pediatric primary thrombocythemia patients, it is recommended to recheck platelet count every 3-6 months. For patients with mild symptoms, a small dose of aspirin [2-3 mg/kg/ day, maximum not exceeding 75 mg]

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can be taken orally, carefully monitoring for complications such as bleeding. High-risk patients can undergo cytoreductive treatment; low-risk patients who fail treatment, have thrombosis, severe bleeding complications, or have excessively high platelet counts are also recommended to undergo cytoreductive treatment. Close monitoring of related toxic side effects is required when using cytoreductive treatment.

Conclusion

During the diagnosis of primary thrombocythemia, a careful search for somatic mutations related to myeloid malignancies or rare germline mutations causing familial thrombocytosis is necessary. The treatment choice is the most challenging issue regarding pediatric thrombocytosis, as current recommendations are primarily based on adult treatment guidelines. Future prospective studies are needed to verify the efficacy and safety of drug treatments. Close platelet count monitoring is appropriate for asymptomatic or mildly symptomatic chronic thrombocytosis patients. Low-dose salicylate preparations may be adequate for children with obvious thromboembolic or bleeding symptoms and related risk factors such as JAK2 V617F mutations. Indications for cytoreductive treatment need careful identification.

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