Essential thrombocythemia: a rare disease in childhood

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Essential thrombocythemia is an acquired myeloproliferative disorder characterized by the proliferation of megakaryocytes in bone marrow, leading to a persistent increase in the number of circulating platelets and thus increasing the risk for thrombotic and hemorrhagic events. The disease features leukocytosis, splenomegaly, vascular occlusive events, hemorrhages and vasomotor disorders. The intricate mechanisms underlying the molecular pathogenesis of this disorder are not completely understood and are still a matter of discussion. Essential thrombocythemia is an extremely rare disorder during childhood. We report on a case of essential thrombocythemia in a child and discuss the diagnostic approach and treatment strategy.

Keywords: *Thrombocythemia, essential/drug therapy; Thrombocytosis; Thrombosis; Myelodysplastic-myeloproliferative diseases; Platelet aggregation inhibitors/therapeutic use; Hydroxyurea/therapeutic use; Humans; Case reports; Female; Child*

Introduction

Essential Thrombocythemia (ET) is an acquired myeloproliferative disorder characterized by a sustained elevation in the platelet count (≥ 450 x 10^9/L) with a tendency for thrombotic and hemorrhagic events during its clinical course[1,2]. An elevated platelet count is related to an expansion of the megakaryocytic lineage; the disorder is usually considered to be a clonal disease arising in a multipotent stem cell.

A recent study has identified a somatic activating mutation resulting in a valine to phenylalanine substitution at position 617 (V617F) in the Janus Kinase 2 gene (JAK2) in 40 to 60% of patients that present with ET[2] but the intricate molecular mechanisms underlying the pathogenesis of this disorder are still a matter of discussion[1].

Prevalence in the general population is approximately 30/100,000 and the reported annual incidence rates range from 0.59 to 2.53/100,000 inhabitants. The median age at diagnosis is 65 to 70 years with the disease affecting women more than men (2:1)[1]. ET is an extremely rare myeloproliferative disorder in childhood[3].

ET is primarily characterized by thrombocytosis. Other characteristics include leukocytosis, splenomegaly, vascular occlusive events (arterial and/or venous thrombosis involving the cerebrovascular, coronary and peripheral circulation), hemorrhages and vasomotor disorders (headaches, visual disorders, lightheadedness, atypical chest pain, distal paresthesia). Approximately one third of patients (36%) are asymptomatic, up to 20% may develop secondary myelofibrosis and 5-10% of cases develop acute leukemia[2,4,5].

We report on the case of ET in an 8-year-old girl with a history of headaches since the age of three.

Case report

An 8-year-old girl was admitted to our pediatric emergency room complaining of a severe headache but presenting no fever, vomiting, weight loss or any other complaints. According to her medical history, she had had recurrent episodes of headaches since the age of three without any apparent trigger. Ocular and primary neurological causes were excluded.

Upon admission, the patient presented no cardiorespiratory symptoms. Except for the headache, she had no other neurological symptoms. Her vital signs were as follows: heart rate: 96 beats/minute; blood pressure: 100 x 70 mmHg; respiratory rate: 18 breaths/minute and temperature: 36°C. The physical examination revealed splenomegaly (6 cm) in left hypochondrium but no adenopathy. Abdominal ultrasound revealed homogeneous splenomegaly (longitudinal diameter 15 cm) and an angiotomography of the central nervous system was normal. Laboratory results were as follows: hemoglobin: 12.3 g/dL; hematocrit: 38%; leukocyte count: 28 x $10^3/\mu$L; platelet count: 1609 x 10^9/L (confirmed in peripheral blood); analysis of coagulation (prothrombin time, activated partial thromboplastin time, fibrinogen and D-dimer), hepatic transaminases, bilirubin and renal function were normal.

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There was no evidence of infection, inflammation, hemolysis or iron deficiency. A hypothetical diagnosis of ET was then proposed and an investigation was undertaken testing platelet aggregation, bone marrow biopsy, the fusion BCR/ABL protein and the JAK2V617F mutation. The platelet aggregation test showed hyperaggregation with epinephrine, collagen and adenosine diphosphate and normal aggregation with ristocetin. The bone marrow biopsy showed megakaryocytic hyperplasia with preserved maturation and atypical megakaryocytes, without changes in the erythrocyte and granulocyte series. Neither fibrosis nor dysplastic changes were observed. The JAK2 mutation (JAK2V617F) was detected in a heterozygous status and the expression of BCR/ABL was negative.

Once ET diagnosis was confirmed, treatment with aspirin was initiated. The patient received 100 mg aspirin (3 mg/kg/day) for five months, without response of the thrombocytosis and headache symptoms. The aspirin was suspended and low dose hydroxyurea was initiated; dose was increased slowly based on control blood tests. The patient is currently asymptomatic, having received the drug over six months at a dose of 20 mg/kg/day. The platelet count started to decrease after 3 months of use, reaching levels under 450 x 10^9/L.

Discussion

Thrombocytosis has several potential etiologies and the evaluation of a patient with this diagnosis therefore requires that the history, comorbidities, other hematologic parameters and past platelet counts are considered. Causes of thrombocytosis can usually be described as spurious, reactive or clonal (Table 1)[6].

Table 1 - Causes of thrombocytosis

Clonal	Reactive	Spurious
Essential thrombocythemia	Infection	Microspherocytes
Polycythemia vera	Inflammation	Neoplastic cell fragments
Primary myelofibrosis	Iron deficiency	Schistocytes
Chronic myeloid leukemia	Hyposplenism	Bacteria
	After surgery	
	Hemolysis	
	Malignancy	
	Effect of drugs	

Source: adapted from Bleeker and Hogen[6]

Spurious thrombocytosis is an extremely rare cause of apparent thrombocytosis and is characterized by the presence of non-platelet structures in the peripheral blood, such as microspherocytes, neoplastic cell fragments, schistocytes or bacteria, which are counted as platelets by automated counters[6].

The most common etiologies of thrombocytosis are reactive causes. Infection, inflammation, tissue damage, chronic inflammatory disorders, hyposplenism, post-operative, iron deficiency, hemolysis and malignancy are the most common causes with one or more of these processes presenting in > 75% of the cases of reactive thrombocytosis[1,6].

Once reactive thrombocytosis is excluded and thrombocytosis is persistent, the diagnosis of a clonal thrombocytosis (myeloproliferative diseases) should be considered. The most common clonal processes associated with thrombocytosis include ET, chronic myeloid leukemia, polycythemia vera and primary myelofibrosis[7].

In 2008, the World Health Organization (WHO) proposed criteria and algorithms for diagnosing myeloproliferative diseases. Diagnosing ET requires the presence of four criteria: platelet count of at least 450 x 10^9/L; bone marrow biopsy specimens showing proliferation, mainly of the megakaryocytic lineage with increased numbers of enlarged mature megakaryocytes and no significant increase or left shift of granulopoiesis or erythropoiesis and identification of a JAK2 mutation or other clonal marker[7].

Diagnosis of ET in children may also require exclusion of manifestations due to hereditary transmission involving genetic defects of the thrombopoietin receptor, thrombopoietin and myeloproliferative leukemia mutations expressed in both somatic and germ line cells[7].

In the case presented, spurious and reactive thrombocytosis were excluded and the patient met all ET criteria established by the WHO.

The treatment strategy is based on the possibility of thrombotic complications and the options are antiplatelet therapy and cytoreductive drugs[6,8]. However, there are no available guidelines for risk stratification in children to help therapeutic decisions[7].

In low risk and asymptomatic adult patients, the indication of antiplatelet therapy is not consensus. A recent publication questions the benefit of low-dose aspirin (100 mg/day) in this group of patients[8]. These investigators concluded that antiplatelet therapy may be associated with a reduction in the incidence of venous thrombosis in JAK2-positive patients and that aspirin may decrease the frequency of arterial thrombotic events in patients with associated cardiovascular risk factors. In JAK2 negative patients with no risk factors, the benefit of aspirin for reducing thrombosis associated with no increase in bleeding is not favorable[8]. The use of this drug is contraindicated in ET patients with extreme thrombocytosis in whom the presence of acquired von Willebrand syndrome may be present[1]. Although there is no consensus in the treatment of low-risk patients, high-risk patients need to be treated with cytoreductive drugs. Cytoreduction aims to bring the platelet number into the normal range in patients with high risk of thrombosis. In patients whose high risk is mainly hemorrhagic, lowering the absolute platelet number greatly under 1000 x 10^9/L should be the main goal[1].

Hydroxyurea is considered a reference platelet lowering agent in high-risk ET patients. A reduced platelet count and its anti-thrombotic activity has been demonstrated in two published, randomized prospective trials concerning the treatment of this category of patient[9]. The recommended starting dose is 15 mg/kg/day; this can be increased to 30 mg/kg/day[9].

Alternative drugs include interferon-alpha and anagrelide. The adverse effects of interferon-alpha, such as flu-like syndrome, neuropsychiatric symptoms and autoimmune phenomena, can be

particularly dangerous for children and anagrelide is not licensed as first-line therapy for ET in Europe and is not approved for use with children[7].

Since interferon-alpha is more effective than hydroxyurea in reducing the rate of thrombosis and anagrelide appears to provide partial protection from thrombosis, particularly in JAK2 V617F-negative ET patients, both may be suitable as second-line therapy for patients in whom hydroxyurea is inadequate or not tolerated[7,10].

In the presented case, even though no protocols for risk stratification and management of this condition in pediatric patients exists, since the patient was symptomatic, presenting with platelet hyperaggregation and acquired von Willebrand disease was ruled out, therapy with aspirin was the initial choice. As no clinical or lab improvements were observed after treatment, aspirin was replaced by hydroxyurea.

The JAK2 mutation status of ET patients cannot, at present, be used for prognosis assessment, vascular risk or clonal progression and trials are needed to establish this relationship[1].

Allogeneic bone marrow transplantation is only discussed for those patients whose condition has transformed into acute leukemia or myelodysplasia or progressed into high risk myelofibrosis[1]. Even in this context, transplantation should be regarded as experimental therapy.

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