Thrombocytosis is not an uncommon entity in children, but it occurs as a reactive change to a variety of conditions. Essential thrombocythaemia is exceedingly rare in the pediatric age group. Among the myeloproliferative disorders in the pediatric age group, chronic myelogenous leukemia (CML) is the commonest, followed by polycythemia vera, essential thrombocyto\(\text{si}a\) (ET), and myelofibrosis (MF). The incidence of essential thrombocythaemia is estimated to range from 1-4 cases per 10 million people younger than 20 years.\(^1\) It can affect any race or sex.

**CASE**

A 13-year-old girl presented with severe, global, rapidly worsening headache of 2 days duration without any history of head trauma, vomiting, fever, seizures, altered sensorium, neck stiffness or weakness in any part of the body. Past medical and surgical history was insignificant. Her physical examination, including central nervous system examination, was unremarkable. For the severe headache, she underwent an MRI of the brain, which showed a partial thrombus of the superior sagittal sinus (SSS) with mild engorgement of the venous channels of both cerebral hemispheres (Figure 1). Subsequently MR venography of the brain confirmed thrombosis of SSS with partial thrombosis of right-sided transverse sinus.

A complete blood count revealed a hemoglobin of 12.5 g/dL, a total leucocyte count of 9×10^9/L, differential count of polymorphonuclear cells 65%, lymphocytes 30%, eosinophils 5%, and platelets of 943×10^9/L. A high platelet count with mild anisocytosis was also appreciated on the peripheral smear examination, which otherwise was unremarkable. Thrombocytosis was assumed to be reactive to thrombosis. Erythrocyte sedimentation rate, blood glucose, liver function tests, kidney function tests and iron profile were all within normal limits. Baseline prothrombin time (PT), activated partial thromboplastin time (aPTT) and fibrinogen levels were normal. The patient was screened for thrombophilia. The results of antithrombin, protein C, protein S, antiphospholipid antibodies, homocysteine levels, apolipoprotein A/B, lupus anticoagulant, antinuclear antibodies were all normal and the patient was started on antithrombotics (subcutaneous low molecular weight heparin followed by Acenocoumarol and antiplatelet agents (aspirin)). On follow up she showed regression of the superior sagittal
sinus thrombosis but thrombocytosis persisted. With no secondary cause apparent for persistent thrombocytosis, we looked for the JAK2 mutation (V617F), BCR-ABL fusion transcript. A bone marrow aspirate and biopsy were also performed. They showed a markedly increased number of mature megakaryocytes with hyperlobulated nuclei (some with a staghorn appearance), focal clustering and platelet pools. Overall, the bone marrow examination was consistent with essential thrombocythaemia (Figure 2, 3, 4). JAK2 mutation and BCR ABL were negative. Family screening for any thrombocytosis was negative. The patient fulfilled all the WHO 2008 diagnostic criteria for essential thrombocythaemia.

**DISCUSSION**

Essential thrombocythaemia in children is of two types: i) familial ii) sporadic (nonfamilial). Familial ET in children are a heterogeneous group of disorders with different molecular abnormalities. Inheritance varies; most familial thrombocythaemia cases due to TPO gene mutations are transmitted in an autosomal dominant manner, some are autosomal recessive and occasionally it can be X-linked recessive. At least two classes of molecular mutations that lead to familial thrombocythosis are known. One involves mutations of the thrombopoietin (TPO) gene that result in increased TPO production by various mechanisms. The other involves mutations of the C-MPL (TPO) receptor gene that somehow constitutively maintains activated signal transduction, leading to continuous signaling for megakaryocytic proliferation. In some families, no specific molecular abnormalities have been detected.

In essential thrombocythaemia, primary and secondary hypercoagulable states frequently lead to thrombot-
ic episodes and to a hemorrhagic tendency. On the basis of experiences in young adults with essential thrombocythemia, these complications may occur less often in children than in adults. Dame and Sutor reported that about 30% of children with essential thrombocythosis had thromboembolic or hemorrhagic complications at the time of diagnosis or later, and that about 20% of initially asymptomatic children had these complications later.\(^2\) These figures are similar to those of adults. Some studies have shown a lower rate of thrombosis.\(^3\)

Bleeding mainly involves the mucous membranes and skin (eg, GI hemorrhage, hemoptysis, post surgical bleeding, bruises, epistaxis). Thrombosis involves both veins and arteries and may affect the cerebral, coronary, and/or mesenteric arteries; the portal vein; and/or the inferior vena cava. A thrombotic event may, in fact, be the presenting symptom of ET. Classic erythromelalgia (throbbing, aching burning of palms and soles) associated with ET and polycythemia rubra vera has not been described in children. The complication rates in familial thrombocythemia are not well described due to its rarity, but both thrombosis and hemorrhage occur.\(^4\)

For adults and some children with ET, various qualitative platelet abnormalities have also been found. Giant, bizarre-shaped platelets are seen on light microscopy. Platelets lack granules or are hypogranular. Often, megakaryocytic fragments are found in the blood smear. The bleeding time is usually normal. Platelet-function study shows loss of primary-wave and secondary-wave aggregation with epinephrine due to loss of membrane alpha-adrenergic receptors (this finding is most helpful in differentiating primary from secondary thrombocythosis). In patients with non-familial primary thrombocythemia, the plasma TPO level has been reported to be in the reference range or mildly elevated, whereas most patients with reactive thrombocythosis have an elevated level of TPO and interleukin (IL)-6 at least at the onset of the thrombocytosis-triggering event. In the familial form of ET, extremely elevated TPO indicates TPO positivity in essential thrombocythemia.\(^5\)

In a child with reactive thrombocytosis, drug therapy is not required. Thrombohemorrhagic complications are exceedingly rare. The indications for treatment and the best treatment of children with ET are currently not known, and guidelines for the management of children with ET are needed. Familial thrombocythemia has a more benign course than sporadic ET. Symptoms patients with ET should receive treatment to lower their platelet count. For pediatric use, anagrelide or hydroxyurea is recommended. In a study by Harrison et al, adult patients (median age, about 60 years) were randomly assigned to receive low-dose aspirin plus hydroxyurea or anagrelide.\(^6\) Significantly more patients in the anagrelide arm than in the hydroxyurea arm reached the study endpoint. The authors concluded that hydroxyurea plus aspirin was more effective than anagrelide plus aspirin in preventing complications in adults with ET. Some recommend cytoreductive treatment for asymptomatic adult patients with platelet counts of more than 1.5 million/micro liter.\(^7\) Radioactive phosphorus should not be used for young patients because of its carcinogenic potential. Use of pharmacologic agents to prevent thrombotic complications in primary ET is controversial, because no laboratory studies offer predictive value in terms of the risk of thrombosis or hemorrhage. Tefferi et al recommend their use in only patients older than 60 years, in individuals with a history of thrombosis, or persons with cardiovascular risk factors, virtually eliminating pediatric patients.\(^8\) Patients who do develop a thrombus should be treated appropriately.

The prognosis of children with ET appears no different from that of adults. Adult patients have near-normal life expectancy because of the low rate of leukemic conversion. However, no child has been monitored long enough for that statement to be applicable to children. The major morbidity factor is the increased risk of thrombohemorrhagic complications.

REFERENCES