Management of Childhood Immune Thrombocytopenic Purpura

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Abstract

Immune Thrombocytopenic Purpura (ITP) is a common benign bleeding disorder in childhood. Several studies indicate that only few children experience serious bleeding while Intracranial Hemorrhage (ICH) is rare, occurring in less than 1%. The diagnosis of ITP is based principally on the history, physical examination, complete blood count which excludes other causes of thrombocytopenia. Bone marrow examination is not necessary in the straightforward cases and mandatory in typical cases. Steroid has been the standard treatment of acute ITP since long time. It was shown that treatment response did not differ significantly between patients treated with Intravenous Immunoglobulin (IVIG) and steroid although a more rapid increase in platelets count was observed after IVIG. ITP in pregnancy necessitates the management of two patients, the mothers and her baby. Chronic ITP occurs in 20-25% of children with acute ITP. Medical management is preferred over splenectomy. This review highlights the management guidelines of childhood ITP.

What Investigations are Required?

The usual presentation is an acute onset of bruising, purpura and petechiae or less commonly with mucosal bleeding from the gum, nose or rectum. The majority of patients (80%) have infection, usually viral within the preceding three weeks. The role of parvovirus B19 infection was demonstrated in 13% of children employing the polymerase chain technique. Affected children are young (peak age, approximately five years) and previously healthy. Boys and girls are equally affected. The peripheral blood normally shows thrombocytopenia (platelets count less than 100,000/ml with large immature giant platelets often seen without other abnormality, although some individuals have a modest relative or absolute lymphocytosis. In 75-80% of cases, the platelets count return to normal within three months according to different series. The clinical course of the disease is marked by the persistence of the thrombocytopenia which becomes chronic in 25% of children and 60% of adults and by a fatal outcome in less than 1% of cases.

What Investigations are Required?

The diagnosis of ITP is based principally on the history, physical examination, complete blood count and examination of the peripheral smear which should exclude other causes of thrombocytopenia. The platelets count is less than 40x10^9/L in approximately 80% of children with ITP and is evident on peripheral blood smear by bizarrely shaped or giant form.

The mean platelets volume (mpv) may not always be elevated in acute ITP but some investigators demonstrated an elevation of mpv in chronic ITP over the control values and the presence of a low or normal mpv in ITP suggesting an aregenerative thrombocytopenia: i.e bone marrow supression or infiltration by leukemia or lymphoma.
Mild peripheral esinophilia may occur in 20% of children but this finding bears no relationship to prognosis and atypical lymphocytes which may be noted suggesting viral infection. Coagulation tests (prothrombine time, partial thromboplastin time and thrombin time) are normal in ITP. These tests are not necessary in straightforward cases. The bleeding time is prolonged in a child with petechiae and purpura and consequent measurement of it is seldom indicated in a child with acute illness. Cytomegalovirus infection should be considered in infants under one year old (perinatally acquired infection) and infectious mononucleosis in older children. There is no need to do coombs test, Antinuclear Factor (ANF) and DNA antibodies. SLE is reported more commonly in adolescent girls and is usually associated with stigmata of the disease. Should bone marrow aspiration be done? The guidelines of the American Society of Hematology state that a bone marrow examination is not required in adults younger than 60 years of age if the presentation is typical. Also, not necessary in children if management involves observation or IVIG. Although it is not mandatory, many pediatric hematologists recommend that an aspiration be performed before starting corticosteroids to rule out a rare case of acute leukemia. A marrow examination is mandatory in patients with atypical cases such as those with lassitude, protracted fever, bone or joint pain, unexplained macrocytosis or neutropenia. An alternative approach is observation without treatment or investigation, especially if the platelet count is above 30x10^9/L and only to perform a bone marrow aspiration if a child fails to remit within two or three weeks.

**Treatment of Acute I.T.P**

The initial treatment of children with typical acute I.T.P remains controversial because the outcome is so good without treatment. The decision whether to treat such children is driven by fear of Intracranial Hemorrhage (ICH). The actual incidence of ICH is less than 1% and generally occurs below platelet counts of 10x10^9/L. The contributing risk factors include head trauma and exposure to anti-platelet drugs. Most ICH occur within the first week of the onset of ITP. In the absence of the evidence, the opinion that hospitalization is appropriate for a child with severe life-threatening bleeding, regardless of the platelet count and for children with platelet count less than 20x10^9/L and mucus membrane bleeding that may require clinical intervention. Also, hospitalization is inappropriate for children with platelet counts less than 20x10^9/L that may be inaccessible or noncompliant or whose parents request hospitalization.

Hospitalization is inappropriate for children with a platelet count of 20-30x10^9/L who is asymptomatic or with count more than 30x10^9/L whom is asymptomatic or has minor purpura. The therapeutic management of acute ITP is a matter of debate for nearly half of century. Initial therapy should rapidly increase the number of circulating platelets in the early phase of the disease. Steroids were the first medication demonstrated to increase platelet counts acutely in ITP and became the standard treatment of this disorder in the 1960s and 1970s. In 1981, Imbach et al observed increase in platelet counts in children with acute and chronic ITP after administration of high dose IVIG. Many studies compared administration of IVIG and steroids for treatment of childhood acute ITP. It was shown that treatment response did not differ significantly between patients treated with IVIG and steroids, although a more rapid increase in platelet counts was observed after IVIG administration. Both IVIG and steroid therapy were shown in a prospective randomized trial to be superior to no treatment in raising the platelet counts.

Recently, a randomized trial has shown that high dose IVIG 1.0g/kg for two days can increase platelet counts more rapidly than doses 0.3gm/kg for two days, in most children with acute ITP within the first 72 hours of treatment. For children with neurological symptoms, internal bleeding and emergency surgery urgent intervention is required with Methylprednisolone 30 mg/kg/day for three days (maximum 1g per day) together with IVIG 1 gm/kg/day for two or three days and an infusion of platelets two to three times the usual amount infused.
Vincristine may be considered part of combination therapy, antifibrinolytic agents such as aminocaproic acid may reduce mucosal bleeding, and recombinant factor VIIa should be considered.\textsuperscript{34} Splenectomy produces remission in about 80\% of patients but should be considered in children only for severe and continued bleeding.\textsuperscript{35} An update of these guidelines 2003 stated that splenectomy is rarely indicated in children with ITP and commented that “Severe lifestyle restrictions, crippling menorrhagia and life threatening hemorrhage may give good reason for the procedure.”\textsuperscript{36}

**ITP in Pregnant Women and Newborn**

The normal platelet count in healthy uncomplicated pregnancies has been described in many studies. It indicated that the platelet count falls by 10\% during uncomplicated pregnancy, with the decline being greatest in the 3\textsuperscript{rd} trimester.\textsuperscript{37,38} The diagnosis of ITP is more difficult during pregnancy because the presentation may closely resemble that of Gestational Thrombocytopenia (GT). Gestational Thrombocytopenia is the most common cause of thrombocytopenia during pregnancy occurring in as many as 5\% of pregnant women at term.\textsuperscript{33,40} The diagnosis of ITP in pregnancy until recently has been considered to be a diagnosis of exclusion; however, with the recent introduction of antigen capture assays, it may now be possible to diagnose ITP by serologic tests. In those with secondary causes of immunologic thrombocytopenia such as systemic lupus erythematosus, HIV and hypogammaglobulinemia certain serologic tests may be required.\textsuperscript{39}

The frequency of neonatal thrombocytopenia in infants born to mothers with ITP was found to be 4\% with platelets count less that 20x10\textsuperscript{9}/L at birth and 10\% with platelets count less that 50x10\textsuperscript{9}/L at birth. Many newborns will have a fall in their platelet count over their first several days of life following delivery with a nadir count at 4-5 days after delivery.\textsuperscript{40}

Percutaneous Umbilical Blood Sampling (PUBS), also known as cordocentesis under ultrasound guide removal of fetal blood from the umbilical vein while in utero.

This technique is difficult and can lead to fetal distress and associated with fetal bleeding and death.\textsuperscript{41} In a recent review of 175 cases of PUBS, severe neonatal thrombocytopenia was recognized in 7\% and the procedure related complication rate was 5\%.\textsuperscript{42} It is not necessary to perform this procedure in mothers with ITP. Fetal scalp sampling is the collection of a small amount of fetal blood via a small scalp incision just before delivery. Analysis of the literature indicates that in about half of the cases, the fetal scalp platelet count differs by as much as 35\% of the true platelet count. This procedure is difficult and it would not change the management, therefore they stopped doing it.\textsuperscript{43,44}

At labor, women with ITP should be delivered by cesarean section in selected circumstances (fetal platelet count is not known). Cesarean section is not indicated when maternal platelet count is more than 50x10\textsuperscript{9}/L. If fetal platelet is known and less than 20x10\textsuperscript{9}/L cesarean section is appropriate. Prophylactic platelet transfusions with IVIG before delivery are appropriate in women with counts less than 10x10\textsuperscript{9}/L. The neonatal platelet count should be measured for 3-4 days after birth. Brain imaging (e.g. ultrasound) should be performed if the platelet count at birth is less that 20x10\textsuperscript{9}/L and appropriate if the count 20-50x10\textsuperscript{9}/L. The treatment of the newborn without evidence of ICH with IVIG is appropriate if the platelet count is less than 20x10\textsuperscript{9}/L. Counts of 20-50x10\textsuperscript{9}/L don’t necessarily require IVIG treatment. Counts more than 50x10\textsuperscript{9}/L should not be treated with steroid or IVIG. Newborn with evidence of ICH should be treated with IVIG and steroid if platelet counts less that 20x10\textsuperscript{9}/L. Women with ITP should not be discouraged from breast feeding.\textsuperscript{8,39}

To date, there is no evidence that maternal therapy will predict rise in fetal platelet count,\textsuperscript{45} but some uncontrolled studies suggest that prednisolone was effective in raising fetal platelet count while others didn’t demonstrate that.\textsuperscript{46,47} IVIG is transported across the placenta but no study has documented that high dose IVIG will raise the fetal platelet count.\textsuperscript{48} The only strong predictor of the severity of neonatal thrombocytopenia has been mothers who have given birth to previously affected infants. Four studies have shown a positive correlation and no studies dispute this relationship.\textsuperscript{49,50}
Chronic ITP

Chronic ITP defined as a platelet count below 100x10^9/L persisting for more than six months from onset of illness, occurs in approximately 20-25% of children with acute ITP. Predictors for chronicity include older age (more than 10 years) and an insidious presentation. Most patients and their families require reassurance together with avoidance of aspirin and contact sports. The only patients with chronic ITP who need treatment are:

1. Those with profound thrombocytopenia and repeated mucosal bleeding.
2. Older children with menorrhagia.
3. Children with accident and trauma.
4. Those needing elective surgery.
5. Those who develop any acute neurological signs.

An alternative treatment with steroid has to be considered in some children with chronic ITP who need treatment. Pulses of high dose Methylprednisolone 30mg/kg/day for three days appear safe and can offer temporarily raise platelet count to cover emergency. This approach offers, perhaps safer and cheaper alternative to IVIG which can be used in similar circumstances. High dose dexamethazone 0.6 mg/kg/day for four days once monthly for six cycles have been tried in children and adult with chronic ITP. Some patients had an excellent response with platelet counts that increased to above 150x10^9/L.

Intravenous Anti-D; in 1983 Salama et al reported platelet response in three of six Rh(D) positive ITP patients treated 400-2500 micro gram of Anti-D. Both Fc-receptor blockade and immunomodulation have been proposed as the mechanism by which anti-D acts. A multicenter study of the treatment of childhood chronic ITP with anti-D found that it is safe, convenient, inexpensive, and effective form of therapy. When treatment is indicated, the initial therapeutic maneuver consisted of an escalating dose of anti-D as follows:

Day 1, 25 mg / kg
Day 2, 25 mg / kg
Day 7, 35 mg / kg
Day 14, 45 mg / kg
Day 21, 55 mg / kg

The anti-D is infused over a 30 min period on an out patient basis. The treatment will be stopped if platelet count rose to more than 150x10^9/L during the course of therapy. A response rate is approximately 90% within one week of treatment; the median duration of response was five weeks. A dose of 75 mg/Kg increases the platelets count more rapidly and for a longer period of time than 50 mg/Kg in adults with ITP. Children with acute ITP receiving 75 mg/Kg/day had overnight platelets increases in seven out of nine cases. The clinical experience is accumulating to indicate that Anti-D is as effective, probably safer and easier to administer than IVIG.

Splenectomy has been used for many years and about two thirds of chronic cases will derive permanent benefit, it should not be considered before at least six months and preferably 12 months from the time of diagnosis, unless there are major problems.

Practice guidelines developed for the American Society of Hematology and published in 1996 are similarly conservative. The indications for elective splenectomy in children with ITP such as persistence of disease 12 months after diagnosis with bleeding symptoms and platelet count below 10x10^9/L (age 3-12 years) or 10-30x10^9/L (age 8-12 years). These guidelines reflect the significant spontaneous remission rate in children with chronic ITP. The laproscopic technique is preferred in those centers with surgeon familiar with this technique. Management of children with chronic ITP who fail to respond or relapse following splenectomy and who manifest symptomatic, severe thrombocytopenia is a real challenge. A search for an accessory spleen should be initiated using appropriate imaging techniques. Therapeutic options include steroid and IVIG whereas anti-D is generally ineffective. The sustained remission rate with monotherapy (azathioprine, cyclophosphamide, vincristine, cyclosporine, danazol, colchicine and interferon alpha) is disappointing and controlled trials have not been performed. A combination therapy may offer the potential of improved outcome such a combination of vincristine 1.5 mg/m2/wk and methylprednisolone 100 mg/m2/wk and oral cyclosporine 5-7 mg/kg twice daily.
An emergency treatment of a child with chronic ITP presented with severe thrombocytopenia and life threatening bleeding include immediate administration of a larger than usual infusion of platelets plus I.V methylprednisolone 30 mg/kg, followed by infusion of 1.0gm/kg of IVIG. This might be repeated for two days. An emergency splenectomy may be considered in children who have not yet had this intervention. Repeat platelet transfusions following administration of IVIG may be beneficial.31,63

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معالجة نقص الصفائح الدموية المناعي عند الأطفال

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وهو إجباري في الحالات الغير واضحة العلاج بالكورتيزون هو الدواء المثالي منذ زمن بعيد وقد بُينت الدراسات أنه لا فرق في النتائج بين اعطاء دواء الكرتيزون أو أميون كلوبيلين، بالرغم أن الصفائح الدموية ترتفع اسرع في حالة اعطاء أميون كلوبيلين.

نقص الصفائح الدموية عند المرأة الحامل يتنام معالجة الأم والرضيع. الحالات المزمنة تحدث بنسبة 20-25% عند الأطفال المصابين بحالات النقص الحاد و إن المعالجة بالأدوية تفضل على المعالجة الجراحية باستئنال الطحال. هذه المرجعة تركز على إرشادات في معالجة الأطفال المصابين بهذا المرض.

ملخص:

نقص الصفائح الدموية المناعي هو حالة مرض ينتج عنه نزف من الأغشية المخاطية والجلد وشائع عند الأطفال. معظم الدراسات تبين أن عدد قليلاً من الأطفال يعانون من نزف شديد وأن حالات نزف الدماغ نادرة جداً وتحدث بنسبة أقل من 1%. تشخيص حالات نقص الصفائح يبنى على أخذ السيرة المرضية، الفحص السريري، فحص الدم الغادي و استثناء المسببات الأخرى لنقص الصفائح الدموية.

إن فحص نخاع العظام غير ضروري في الحالات الواضحة.