SPECIAL ARTICLE

ADULT IDIOPATHIC THROMBOCYTOPENIC PURPURA – AN OVERVIEW

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SINGAPORE MED J 1995; Vol 36: 355-356

Idiopathic thrombocytopenic purpura (ITP) is an immunoregulatory disorder in which antibodies damage platelets leading to their removal by the cells of the reticuloendothelial system (RES). This occurs mainly in the spleen which is also regarded as the primary site of synthesis of these antiplatelet antibodies. ITP occurs both in the acute and chronic forms, the former usually in children and the latter, in adults. Eighty to 90% of children who develop acute ITP have a spontaneous remission within 6 to 12 months. This is not the case with adult ITP where spontaneous remissions are uncommon. In the series reported in this issue, no case of spontaneous recovery was observed in a cohort of 37 patients[1]. ITP is a disease of unknown aetiology although a viral infection is often implicated[1]. Acute ITP has been reported following infectious mononucleosis and the childhood exanthemata[2]. More recently, ITP has been reported in persons infected with the human immunodeficiency virus and patients with clinical acquired immunodeficiency syndrome. Other conditions associated with ITP include Wiskott Aldrich syndrome and autoimmune and lymphoproliferative diseases. Harrington was the first to demonstrate the presence of a humoral factor in ITP patients which, when transferred into volunteer normal individuals, resulted in a precipitous fall in their platelet counts [3]. ITP is now considered an autoimmoune disease [4,5].

Clinically, patients with ITP present with recurrent, usually spontaneous, purpurae and mucous membrane haemorrhages. Frank bleeding, such as epistaxis, haematuria, menorrhagia and gastrointestinal bleeding, occurs in the more severe cases. Intracranial haemorrhage is rarely seen and is a major cause of death. Clinical features of remark are petichiae, purpurae and painless ecchymoses in the skin and blood blisters in the buccal mucosal surface. Splenomegaly and lymphadenopathy are uncommon and their presence should make one suspect the thrombocytopenia to be due to other diseases like leukaemia and the lymphoproliferative disorders.

Diagnosis of ITP is by exclusion of other causes of thrombocytopenia. A low platelet count and an increase in bone marrow Type I and II megakaryocytes are the main features. There may also be features of iron deficiency anaemia due to blood loss. Antiplatelet antibodies have been demonstrated by techniques such as Platelet Factor 3 availability after immunoinjury, histochemical change with immunoperoxidase, 14C 5-hydroxytryptamine release and presence of platelet-associated immunoglobulins (PA IgG and PA IgM) attached to platelets. Circulating antiplatelet antibodies have also been demonstrated by flow cytometric analysis [6]. Laboratory investigations to exclude other autoimmune diseases like systemic lupus erythematosus (SLE) and platelet consumption due to disseminated intravascular coagulopathy (DIVC) should also be done. As ITP has been reported in patients with lung and kidney cancers, not due to DIVC associated with these conditions, it is important that a chest X-ray and abdominal CT-scan be done when ITP suddenly presents in patients in the cancer risk age-groups for these malignancies.

The treatment of ITP involves three considerations: 1) the management of bleeding, 2) the control of antiplatelet antibody production and antibody-mediated platelet destruction by the RES, and 3) further management of chronic refractory disease.

Bleeding is often the presenting symptom in most patients. This may be in the form of cosmetically undesirable lesions or problematic haemorrhaging such as menorrhagia. Platelet transfusions are helpful but have attendant problems such as production of isoagglutinins and rapid sequestration of transfused donor platelets. Some of these difficulties have been overcome by using single donor cell-separator harvested platelets or massive pre-transfusion of effete platelets to "mop up" the antiplatelet antibodies prior to administration of physiologically functional fresh platelet concentrates. Antifibrinolytic agents have also been found to be effective in a limited way.

Measures that decrease the production of antiplatelet antibodies or reduce their damaging effects include the use of immunosuppressive agents and splenectomy. Corticosteroids (prednisolone) and splenectomy are the mainstays of ITP therapy. Prednisolone not only reduces the production of antiplatelet antibodies by the RES cells but also blocks the phagocytosis of antibody-damaged platelets by them. The disadvantages of using prednisolone are the unpleasant side effects and the delays in getting a response. Splenectomy is more effective but results are sometimes unpredictable. One reason for this is that the spleen may not be the main site of platelet sequestration. Although this may be determined by using isotope-labelled platelets in pre-surgery scanning studies, the technique is cumbersome and not readily available. In most series, the overall response rate with complete remission to splenectomy is approximately 70% but up to 95% have an improvement in the overall clinical situation with some increase in platelet counts and a lessening of the bleeding tendency so that further medical treatment is not required. In the series reported here, the response rate to splenectomy is significantly low at 25% [1]. The explanation given by the author of patient reluctance for surgery leading to alternative treatment with second-line immunosuppressive agents, usually reserved for splenectomy-failed patients elsewhere, should be noted. Splenectomy results in nonreversible immune suppression and is preferably avoided in patients with a high likelihood of a spontaneous remission. Death after splenectomy has been reported as one of three major causes of mortality together with intracranial haemorrhage and infection

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after cytotoxic treatment[7]. The timing for splenectomy remains controversial [8]. It is therefore contraindicated in children.

Intravenous immunoglobulin was first demonstrated to be useful in ITP by Imbach after he observed an increase in the platelet counts of children with the Wiskott Aldrich syndrome who were given i.v. immunoglobulin for immune deficiency [9]. This was followed by similar reports from Carrol and Vos [10,11]. In all of these series, the initial study dose of the i.v. immunoglobulin was high at 5 x 0.4 gm of intact 7S IgG/kg body weight but Toh et al reported equally good responses with a low dose regime of 3 x 0.2 gm/kg body weight [12]. Imbach has recently reported successful results with a low dose regime of 2 x 0.4 gm/kg body weight with the majority of his patients [5]. This has economic implications for the developing countries. The mechanism of action of i.v. immunoglobulin appears to be via interference of splenic Fc receptor mediated immune clearance of antibody-coated platelets.

The chronic ITP patient presents special problems. Many who failed corticosteroids or splenctomy have been given other antineoplastic and immunosuppressive agents. Vincristine and vinblastine have been used with effect by Ahn [13]. Both agents can be given as bolus injections or after incubation with platelets used for transfusion. Azathioprine and cyclophosphamide are also effective but note should be taken of their mutagenic effects and the possible development of malignancies in patients exposed to these agents. Danazol has also been used but has unpleasant masculinising side-effects. Despite all measures, there remains a number of patients with ITP who run a refractory course. These may subsequently evolve into Evan's syndrome with associated autoimmune haemolytic anaemia or become part of a wider spectrum autoimmune disease like SLE. The author of the article in this issue has noted that the ITP becomes more responsive to corticosteroid when this is intensified to treat the emerging SLE or autoimmune haemolysis [1]. This change in sensitivity may be regarded as a form of competitive inhibition of the RES Fc receptor sites by the SLE immune complexes and antibody-coated erythrocytes in the Evan's syndrome. Finally, attending physicians are sometimes presented the problem of what next to do with a thrombocytopenic patient whose platelet counts remain low despite all efforts at treatment. A good guideline to adopt is to approach the refractory patient in the clinical context and not to aim at increasing platelet counts per se at the cost of life-threatening morbidity from the side-effects of medication. One should treat the patient rather than the platelet counts and just observe matters if there is no bleeding, even if the platelet counts are suboptimal. Recent reports have, however, shown resistant ITP to respond to pulsed high-dose dexamethasone and interferon [14,15].

There remains a category of patients with ITP who have special problems. Like all autoimmune diseases, ITP affects females twice or thrice as frequently as males. There is no contraindication to a woman with ITP having a child provided these special problems are attended to. It is well to remember that a patient in remission following splenectomy may still have antiplatelet antibodies. Pregnancy itself may cause a relapse or exacerbate existing ITP. The use of mutagenic immunosuppressive agents is contraindicated. Corticosteroids may cause maternal diabetes mellitus and eclampsia. Infant mortality is increased and may be due to hypoadrenalism and bleeding, as antiplatelet antibodies cross the placenta. It is best to let birth be by vaginal delivery although a slight chance of intracranial bleeding in the neonate is present. For this reason, Karpatkin has suggested that steroids be given for at least 2 weeks before expected delivery even if the mother is in remission as it will increase the foetal platelet counts [16]. The alternative is to use i.v. gammaglobulin as this will increase the platelets more rapidly and maintain the response for about 2 weeks. It will come in useful if emergency Caesarean delivery has to be considered for any indication. There is some suggestion that Caesarean birth must be considered if the foetal scalp vein platelet count is less than 5000/cu mm. Post delivery, the neonatal platelet count may remain low for up to 3 weeks before recovering to normal. Neonatal thrombocytopenia can be managed by platelet transfusion or the administration of steroids.

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