Annotations

Idiopathic thrombocytopenic purpura—where do we stand?

How best to manage idiopathic thrombocytopenic purpura, particularly the chronic variety, remains one of the great unsolved mysteries of paediatrics. New ways are still being suggested, as in this issue of the *Archives*,¹ so it is perhaps timely to reflect that if the need for adventurous treatment in patients with persistent thrombocytopenia is accepted uncritically, there is a real danger that many of them could eventually suffer more from the treatment than the disease.

Just what idiopathic thrombocytopenic purpura is and what its morbidity and mortality amount to are important questions not nearly as satisfactorily answered as might be supposed superficially. There are three reasons for this. Firstly, it is a rare problem. The annual incidence of the clinically symptomatic syndrome seems to be around 4 per 100 000 children,^{2,3} which is of the same order of frequency as acute leukaemia; but, unlike that condition, as cases of idiopathic thrombocytopenic purpura are seldom referred for centralised management, experience has accumulated very slowly. Secondly, it is not a specific condition but a heterogeneous group of disorders with a variety of causes and a variable clinical pattern. Thirdly, early studies, or those containing patients diagnosed 20 years ago or more, may have given rise to distorted mortality estimates by failing to exclude patients with other much more serious but now recognised distinct conditions such as thrombotic thrombocytopenic purpura or disseminated intravascular coagulation.^{4,5} Before deciding how to treat a patient, then, it is important to establish as firm a diagnostic base as possible and to be aware of the likely course of the untreated disease.

Diagnosis

Idiopathic thrombocytopenic purpura may be cautiously defined as an acquired thrombocytopenia due to immune mediated shortened platelet survival which occurs as an isolated phenomenon unassociated with drugs or other disturbances of haemostasis or coagulation. The diagnosis is essentially made by exclusion, and to avoid delayed or inappropriate

treatment the more sinister conditions such as leukaemia, marrow hypoplasia, and consumption coagulopathy should be dismissed at the outset. To this end a bone marrow aspirate, preferably with a trephine biopsy, and a disseminated intravascular coagulation screen are minimal initial investigations together with careful examination of the peripheral blood. The presence of autoantibodies to tissues other than platelets may be the only indicator of more serious multisystem autoimmune disease in its early stages and should be looked for. Infectious mononucleosis should also be considered. Positive laboratory findings are not so helpful. Though frequently reported, increased numbers and immature appearances of marrow megakaryocytes are too subjective to be of any value. Platelet antibodies, as indicated by increased platelet associated IgG, may usually be found in both the acute and chronic disorder,⁶ but care should be taken in interpreting results as techniques vary and positive findings occur in diseases other than idiopathic thrombocytopenic purpura.

Prognosis

Over 90% of cases can be expected to resolve spontaneously, mostly within six months, but over 10% may do so over a year later.² It is traditional to divide patients into two clinical groups; those with the more common acute syndrome seen in the younger child with a sudden spectacular onset and (usually) a rapid spontaneous resolution, and those with the chronic variety seen in the older patient where the onset is more insidious. Some 10% will fall into the latter group,⁷ but the distinction between the two is less than perfect and so of limited value in predicting confidently the course of the disease in a given patient.² Platelet antibody studies have not helped much in this respect;⁸ nor have other candidate prognostic variables such as the number of eosinophils in the marrow² or a history of antecedent upper respiratory tract infection, which can be obtained from most children. Idiopathic thrombocytopenia after specific fevers such as

rubella or varicella is usually of the acute self limiting type.

The chief prognostic concern is undoubtedly life threatening haemorrhage developing while a child is profoundly thrombocytopenic, but the possibility of this should not be overestimated. The incidence is difficult to determine accurately but it is very small, and if cases of disseminated intravascular coagulation and thrombotic thrombocytopenic purpura are rigorously excluded, is probably less than one per cent.^{2 7 9 10} Nonetheless, the prospect of such a catastrophe, however remote, naturally excites anxiety and is one of the chief stimulants to clinicians favouring active as opposed to conservative management. They would doubtless go on to point out that although most intracranial bleeds have arisen in the first few days or weeks of the illness, anecdotal reports exist of examples as late as a year after diagnosis.¹¹ Again, the risk of such late haemorrhage must be kept clearly in perspective and it should be appreciated that persistent uncomplicated idiopathic thrombocytopenic purpura usually remains essentially asymptomatic and may do so for many years even when the platelet count is very low.²

For the longer term outlook it is worth noting that the chronic disease, whether it resolves or not, does not show any tendency to progress to multisystem autoimmunity, nor is there an excess of these disorders in patients' immediate families.²

Management

Given a rare heterogeneous disease that usually (sooner or later) gets better on its own, gives rise to little morbidity even if it does not, and has such a low mortality that the diagnosis should be seriously questioned in any patient who dies, it is not surprising that views on management are based more on clinical impressions and anecdotes than on results of clinical trials.

For the newly diagnosed patient the chief debate centres around the immediate use of steroids. Most^{2 10 12} but not all⁷ authors conclude that steroids should be given, and some merely indicate that they provide no measurable benefit.^{13 14} The clinician is therefore left to make up his own mind, but as there have been no reports of harm after a two to four week course this would seem a reasonable thing to prescribe. Longer term treatment, on the other hand, is universally condemned irrespective of whether the condition resolves or progresses to chronicity.

Severe chronic idiopathic thrombocytopenic purpura presents the main management problem.

Splenectomy is still advised,¹⁵ and can be expected to be associated with a prolonged rise in the circulating platelet count in at least two thirds of patients.^{2 13} But at what price? Increasing awareness of sepsis after splenectomy has made the operation far less attractive as a therapeutic manoeuvre, and in the case of idiopathic thrombocytopenic purpura it may have a mortality in excess of the disease it is being used to beat.¹⁶ A variety of immunosuppressive (that is cytotoxic) drugs has been tried in various ways,¹⁷ but as with splenectomy these treatments may be worse than the disease, and it is doubtful if any are of much practical value in children.

High dose intravenous immunoglobulin has recently been shown to be effective¹⁸ but usually provides transient benefit only and may be accompanied by all the potential problems of large pool blood product treatment such as the transmission of non-A, non-B hepatitis.¹⁹ Nonetheless, such hazards may be acceptable in an emergency and this method of treatment, with its rapid effect, may prove useful for the management of trauma, surgery, or life threatening haemorrhage in those with severe thrombocytopenia.

The search for alternative treatments continues. Danazol, a non-virilising synthetic androgen, has been reported to raise the platelet count in a group of adult patients with chronic idiopathic thrombocytopenic purpura,²⁰ but how it works, whether it always does, and whether its usefulness extends to children is not yet known. Now pulse methylprednisolone is suggested on the basis of two case reports in this issue of the *Archives*.¹ Its usefulness in a larger number of patients has obviously yet to be evaluated, and it may turn out merely to be long term steroid treatment in disguise if the pulses of treatment have to be repeated with any frequency to maintain an effect. Nevertheless, three months unmaintained remission after a single course is encouraging if it is a true response and not a coincidental late spontaneous resolution.

What can be concluded from all this? Undoubtedly the most important facts to bear in mind are that idiopathic thrombocytopenic purpura is generally a benign disorder and no treatment so far described has demonstrably improved the prognosis. Unfortunately, it is unlikely that one ever will, if a statistically significant reduction in life threatening bleeding is the yardstick, as it has been estimated that it would need a randomised trial with 3600 patients in each arm to detect a 50% improvement in this respect.²¹ Treatments to simply raise the chronically depressed platelet count as an alternative, less direct goal should be applied with care. Of those that have been shown to

be effective, none have yet been proved unequivocally to be safer than leaving the patient alone.

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