

## Personal practice

# Chronic idiopathic thrombocytopenic purpura: primum non nocere

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The vast majority of children with idiopathic thrombocytopenic purpura, dramatic though their signs may be at presentation, remit within weeks, with or perhaps despite medical attention. Such children, when referred to the Queen Elizabeth Hospital, Hackney Road by their family doctor, or appearing in the busy casualty department, have a careful history taken with particular emphasis given to the length of history, antecedent infections, and drugs. They are examined for evidence of bleeding, injury, enlargement of lymph nodes, liver, and spleen. A full blood count and coagulation screen are performed and the film is carefully examined. If there is the slightest doubt about the diagnosis or if specific treatment is contemplated a bone marrow aspiration is performed. Treatment involves a period of relative rest and the avoidance of aspirin. The parents are told that this is not leukaemia, that the risk of serious bleeding is very low, and that most children improve spontaneously within weeks to months. A follow up appointment is given to facilitate further discussion. Further active treatment is rarely indicated.

The debate about steroid treatment in acute idiopathic thrombocytopenic purpura<sup>1,2</sup> has to a large extent been supplanted by that about the benefits of intravenous immunoglobulin,<sup>3,4</sup> now alas widely advertised as desirable treatment for acute idiopathic thrombocytopenic purpura. As the mortality of acute idiopathic thrombocytopenic purpura is less than 1% it would take a controlled trial of at least 14 000 patients to show a significant reduction in mortality,<sup>5</sup> and estimation of morbidity is difficult when symptoms usually remit before any alteration in platelet count. It is thus regrettable that a recent clinical trial comparing intravenous immunoglobulin and steroids did not include a control arm.<sup>4,6</sup> While it may be justifiable to give steroids or immunoglobulin (or both) as a *short term measure* to a child with serious bleeding or extensive

mucous membrane haemorrhage at presentation, there is no firm evidence that either is beneficial or, as has been claimed, decreases the risk of chronic thrombocytopenia. Intravenous immunoglobulin is extremely expensive (approximately £30 per gram or £720 per course for a 15 kg child) and although heat treated, carries the theoretical risk of transmission of viral infections, particularly non-A non-B hepatitis.<sup>7</sup>

## Chronic thrombocytopenia

Most children seen in a district hospital have acute thrombocytopenia. In the more rarefied atmosphere of the referral centre there appears a steady trickle of children with chronic thrombocytopenia. This somewhat arbitrary definition is traditionally applied to children with symptoms of longer than six months. The story of such patients is usually a variation on one of two themes. Either the child has a long history of easy bruising and eventually a blood count is performed and shows thrombocytopenia or there has been an acute onset, treatment with steroids, and apparent clinical improvements. After three or four weeks an attempt to reduce the steroids is followed by recurrence of bruising or perhaps just a fall in platelet count. Thus develops a repetitive cycle in which steroids are decreased and increased according to the platelet count, the parents become more anxious and the child more moody and cushingoid. A variation on the second theme is that steroids have been replaced by periodic intravenous immunoglobulin that may produce a temporary rise in platelet count. The management of these patients and their parents is a delicate task, requiring ample time for discussion and reassurance about anxieties which are, I am afraid, frequently iatrogenic.

It is obviously essential to be confident of the diagnosis. A story of bruising since infancy should

prompt suspicion of one of the rare congenital thrombocytopenias, many of which present with low platelets and a cellular marrow with abundant megakaryocytes.<sup>8</sup> A careful inspection of the blood film, and when appropriate, tests of platelet function should exclude such a diagnosis. The finding of Döhle bodies in the neutrophils is a feature of the May-Hegglin anomaly, a rare autosomal dominant disorder associated with mild thrombocytopenia while small platelets with a history of affected males may suggest a forme fruste of Wiskott-Aldrich syndrome. The blood film in idiopathic thrombocytopenic purpura shows large platelets but the presence of numerous giant forms should arouse suspicion of the Bernard-Soulier syndrome, an autosomal recessive disorder of platelet function characterised by variable thrombocytopenia and by defective platelet aggregation with the antibiotic ristocetin.

Bone marrow examination is essential in the assessment of the child with chronic thrombocytopenia. If adequate slides are not available for review then an aspirate must be performed; if the slide does not show adequate megakaryocytes a trephine should be performed to assess marrow cellularity. Aplastic anaemia is rare in childhood but, particularly in the congenital marrow failures such as Fanconi's anaemia and dyskeratosis congenita thrombocytopenia may be the only abnormality in the blood count for many years.<sup>9</sup> The congenital abnormalities may be subtle or even absent in Fanconi's anaemia and mucosal atrophy and dystrophic nails often defy diagnosis in early dyskeratosis congenita. Once these conditions have been excluded how useful are other investigations in chronic thrombocytopenic purpura? Platelet associated immunoglobulin is raised in the vast majority of children with chronic idiopathic thrombocytopenic purpura but the availability of platelet serology has had little impact on the selection of treatment.<sup>10</sup> It is important, particularly in the older child, to investigate for the presence of other autoimmune disorders. While some children with chronic idiopathic thrombocytopenic purpura have subtle laboratory evidence of an immunoregulatory disorder few develop systemic lupus erythematosus or autoimmune haemolytic anaemia.<sup>11</sup>

### **Management of chronic idiopathic thrombocytopenic purpura**

Chronic idiopathic thrombocytopenic purpura is usually a benign condition which does not require specific treatment and may remit at any time. Fifteen of a group of 150 children in Cleveland were

still thrombocytopenic after one year but 11 of the 15 were asymptomatic and nine underwent spontaneous remission after two to 20 years.<sup>12</sup> There were no episodes of intracranial haemorrhage. In a long term study from Newcastle, 22 of 123 children remitted after one year, and three after five years.<sup>13</sup> There were two episodes of intracranial haemorrhage: one in retrospect due to probable consumptive coagulopathy and the other in a child with acute idiopathic thrombocytopenic purpura who was receiving steroids.<sup>13</sup> These reports reinforce clinical impressions of the natural history of chronic idiopathic thrombocytopenic purpura, but because they emanate from referral centres, probably underestimate the proportion of cases undergoing early remission.

Once the diagnosis is confirmed my main preoccupation is to thus ensure that the family has a reasonable understanding of the disease and this involves careful review of the natural history and treatment options. I reiterate that idiopathic thrombocytopenic purpura is a benign, although alarming, condition and that serious internal haemorrhage is extremely rare and, in my experience, usually seen in the child with haemorrhagic symptoms at onset. It is good if parents can avoid an obsession, often I am afraid iatrogenic, with the significance of minor variations in the platelet count. I emphasise that treatment should be directed at the patient rather than the platelet count, and that frequent blood tests are best avoided. It is also useful to discuss the risk of bleeding in relation to platelet count and to point out that this risk, because of good platelet function,<sup>14</sup> is low in idiopathic thrombocytopenic purpura. I explain that the natural history of idiopathic thrombocytopenic purpura is such that patients may improve spontaneously even after years and that any form of treatment is symptomatic rather than curative. Given this low mortality and spontaneous remission a careful analysis of risk and benefits of treatment is essential.

Most parents and children who have experienced long term treatment with steroids are only too aware of the side effects and anxious to avoid them at all costs. Such treatment has no place in the management of chronic idiopathic thrombocytopenic purpura. Periodic infusions of immunoglobulin have been proposed in the responsive child, as a long term treatment but there is no justification for their routine use.<sup>15 16</sup> Most children need no specific treatment but should avoid aspirin and bodily contact sports. I would recommend short term steroids or immunoglobulin infusions only in the event of overt bleeding or in preparation for surgery. Other forms of treatment, such as vin-

cristine and immunosuppressive drugs, have had their proponents, usually as treatment for symptomatic patients who have not responded to splenectomy, and the reader is referred to an excellent review by Buchanan for an analysis of their lack of benefit.<sup>17</sup> I have no personal experience of any of these measures except in a very few children whose thrombocytopenia is part of a more generalised autoimmune disorder. They have no place in the management of chronic idiopathic thrombocytopenic purpura. Recent reports suggest that danazol, an attenuated androgen, may benefit some patients but further studies are needed.<sup>18</sup>

What then are the indications for splenectomy, the earliest and most established form of treatment for chronic idiopathic thrombocytopenic purpura? It is unfortunate for paediatric practice that splenectomy is regarded by haematologists as a treatment of choice in adults with chronic idiopathic thrombocytopenic purpura refractory to steroids.<sup>19</sup> This thinking has in the past led to many referrals for consideration of splenectomy if a child has not remitted within six months. In view of the mild symptoms of most patients and the significant and indefinite risk of sepsis with pneumococcus and *Haemophilus influenzae*,<sup>20</sup> a decision to recommend splenectomy should only be undertaken after very serious consideration. The risk of postsplenectomy sepsis is in most patients greater than the risk of serious bleeding.

While splenectomy, by removing a major source of synthesis of antibody and an important site of platelet destruction,<sup>19</sup> does result in an improved count in many patients it does not cure the underlying problem. It has been estimated that half of the children with idiopathic thrombocytopenic purpura will achieve normal counts after splenectomy<sup>17</sup> but this clearly depends on the indications. I recommend it very rarely, usually in the older child with repeated episodes of haemorrhage for which there is no local cause. While it seems that children who in the past have had a prompt response to steroids or intravenous immunoglobulin are those most likely to have sustained improvement, the response is not always predictable and it is important to explain that splenectomy usually produces at least a modest improvement in symptoms but that this is not invariable. Preoperative pneumococcal vaccine and postoperative penicillin are recommended. A review of the literature would suggest that the risk of sepsis after splenectomy may actually be greater than that of intracranial haemorrhage,<sup>17</sup> so the decision requires great thought.

Perhaps the most important factor in dealing with the child with idiopathic thrombocytopenic purpura is the attitude of the physician. He must listen to the

very real anxieties and explain in understandable terms the risks and benefits of treatment. With this support most children with chronic idiopathic thrombocytopenic purpura can be managed without specific treatment until their disease undergoes spontaneous remission.

#### References

- McClure PD. Idiopathic thrombocytopenic purpura in children. *Am J Dis Child* 1977;**131**:357-9.
- Zuelzer WW, Lusher JM. Childhood idiopathic thrombocytopenic purpura. *Am J Dis Child* 1977;**131**:360-2.
- Imbach P, Barandun S, d'Apuzzo V, et al. High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. *Lancet* 1981;ii:1228-31.
- Imbach P, Wagner HP, Berchtold W, et al. Intravenous immunoglobulin versus oral corticosteroids in acute immune thrombocytopenic purpura in childhood. *Lancet* 1985;ii:464-8.
- Krivit W, Tate D, White JG, Robison LL. Idiopathic thrombocytopenic purpura and intracranial haemorrhage. *Pediatrics* 1981;**67**:570-1.
- Ekert H. Intravenous immunoglobulin versus oral corticosteroids in acute immune thrombocytopenic purpura in childhood. *Lancet* 1985;ii:1310.
- Lever AML, Brown D, Webster ADB, Thomas HC. Non-A, non-B hepatitis occurring in agammaglobulinaemic patients after intravenous immunoglobulin. *Lancet* 1984;ii:1062-4.
- Stuart MJ, Kelton JG. The platelet: quantitative and qualitative abnormalities. In: Nathan DG, Oski FA, eds. *Hematology of infancy and childhood*. Philadelphia: WB Saunders, 1987: 1343-463.
- Alter BP. The bone marrow failure syndromes. In: Nathan DG, Oski FA, eds. *Hematology of infancy and childhood*. Philadelphia: WB Saunders, 1987:159-241.
- Harrington WJ. Are platelet-antibody tests worthwhile? *N Engl J Med* 1987;**316**:211-2.
- McIntosh S, Johnson C, Hartigan P, Baumgarten A, Dwyer JM. Immunoregulatory abnormalities in children with thrombocytopenic purpura. *J Pediatr* 1981;**99**:525-30.
- Ramos ME, Newman AJ, Gross S. Chronic thrombocytopenia in childhood. *J Pediatr* 1978;**92**:584-6.
- Walker RW, Walker W. Idiopathic thrombocytopenia, initial illness and long term follow up. *Arch Dis Child* 1984;**59**:316-22.
- Harker LA, Slitcher SJ. The bleeding time as a screening test for evaluation of platelet function. *N Engl J Med* 1972;**287**:155-9.
- Bussell JB, Kimberley RP, Inman RD, et al. Intravenous gammaglobulin treatment of chronic idiopathic thrombocytopenic purpura. *Blood* 1983;**62**:480-6.
- Bussell JB, Schulman I, Hilgartner MW, Barandun S. Intravenous use of gammaglobulin in the treatment of chronic immune thrombocytopenic purpura as a means to defer splenectomy. *J Pediatr* 1983;**103**:651-4.
- Buchanan GR. The nontreatment of childhood idiopathic thrombocytopenic purpura. *Eur J Pediatr* 1987;**146**:107-12.
- Weinblatt ME, Kochen J, Ortega J. Danazol for children with immune thrombocytopenic purpura. *Am J Dis Child* 1988;**142**: 1317-9.
- McMillan R. Chronic idiopathic thrombocytopenic purpura. *N Engl J Med* 1981;**304**:1135-47.
- Anonymous. Splenectomy—a long-term risk of infection. *Lancet* 1985;ii:928-9.

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