Severe aplastic anaemia

Now that leukaemia can, in most cases, be treated with some degree of success, severe aplastic anaemia is the most serious blood disorder of childhood. Patients present with pallor and purpura due to anaemia and thrombocytopenia. Other signs and symptoms depend on the aetiology. The disease is more severe in children than adults.

Congenital marrow aplasia

Fanconi's anaemia is the commonest type. It is characterised by multiple congenital abnormalities that vary from patient to patient; but 50% or more show general or localised skin pigmentation, skeletal abnormalities (particularly of the hand and forearm), poor growth, and microcephaly. The chromosomes may show breaks, reunion figures, ring and dicentric chromosomes, acentric fragments, or endoreduplication. These changes may not always be seen in direct lymphocyte cultures, and are best shown by culturing the cells with deoxyribonucleic acid (DNA) crosslinking agents such as mitomycin C. All these abnormalities are present at birth; but the bone marrow disease does not usually cause symptoms until the child is at least 2 or 3 years old. Bruising due to thrombocytopenia is usually the presenting feature. The red cells may be macrocytic; but later anaemia and leucopenia develop. There is a defect of DNA repair, and bone marrow failure progresses insidiously. Patients are more than usually prone to develop leukaemia (often myelomonocytic) and other cancers. Treatment may induce a temporary improvement but most cases eventually become resistant and death ultimately ensues. Heterozygotes for this disease may sometimes show minor signs similar to those seen in patients. Some may also have chromosome abnormalities. It has been claimed that the heterozygotes are predisposed to malignant disease too. Other congenital disorders associated with bone marrow failure include dyskeratosis congenita, the amegakaryocytic thrombocytopenia/aplastic anaemia syndrome, and the Schwachman-Diamond syndrome. Occasional cases of congenital aplastic anaemia are not associated with any other abnormality.

Acquired bone marrow failure

Acquired aplastic anaemia develops in children who were previously well. There are rarely any diagnostic features. The disease develops because the haemopoietic stem cells in the bone marrow are damaged, or changes occur in the mechanisms controlling their differentiation or the bone marrow microenvironment. Chloramphenicol and thiamphenicol, gold salts, sulphonamides, and anticonvulsants may be responsible, as well as chemicals such as benzene, insecticides and DDT, and the agents used by 'glue-sniffers'. Hepatitis of all types may be followed by severe marrow aplasia; but cases have occasionally been described after measles, mumps, infectious mononucleosis, and congenital rubella. It is possible that other low grade viral infections may provoke the disease as commonly occurs in children with acute thrombocytopenia and acquired haemolytic anaemia. An immune mechanism may sometimes be responsible. The patients' bone marrow lymphocytes or peripheral blood lymphocytes may exercise an inhibitory effect on the replication of bone marrow cells. Aplastic anaemia may develop as a complication of graft versus host disease.

Occasionally a child with acute leukaemia presents with pancytopenia and a marrow aspirate which is hypocellular, showing many small lymphoid cells which look like blasts or mature lymphocytes. Lymphadenopathy or splenomegaly are signs of a likely leukaemia. A trephine biopsy will distinguish the two conditions. The marrow should be stained with periodic acid-Schiff stain: coarse granules or blocks indicate acute lymphoblastic leukaemia, as do lymphocyte markers positive for the common acute lymphoblastic leukaemia antigen.

Investigation

Severe aplastic anaemia may rapidly progress to a fatal conclusion. It is important to distinguish urgently congenital from acquired disease: the genetic implications are vital. Any child with profound pancytopenia must have an urgent bone marrow examination. To minimise sampling errors, my practice is to aspirate marrow from two separate sites and take a trephine from the posterior iliac crest using a Jamshidi needle. I prefer general anaesthesia, which need only take a few minutes. The full investigations have been described previously but after a thorough clinical examination to look for stigmata of Fanconi's anaemia, the most useful tests include chromosome analysis with and without mitomycin C; head circumference; intravenous pyelogram; and radiography of long bones including forearms, wrists, and hands. As
bone marrow transplantation may be needed, blood group and HLA studies on the patient and family must be done as soon as possible.

**Treatment and prognosis**

The prognosis is related to the severity of the disease, and a variety of scoring systems have been introduced.\(^1\)\(^6\)\(^7\) Camitta’s scheme is simple: a count of less than 0.5 granulocytes \(\times 10^9/\text{l}\) (<500 per \(\mu\text{l}\)), less than 0.2 \(\times 10^9/\text{l}\) platelets (<20 000 per \(\mu\text{l}\)), and reticulocytes of less than 1% indicate severe disease.\(^7\) There is no easy cure. For the best results, patients need skilled support and should be treated in a specialist centre. In the 1950s and 60s without such support, less than 5% survived. Non-virilising androgens have been widely used. Oxymetholone has been popular, but comparative trials in adults have shown that a dose of 2.5 mg/kg per day is less effective than methandrostroenolone 1 mg/kg per day or norethandrolone 1 mg/kg per day.\(^8\) Mild cases may respond: but in severe disease the results are disappointing.\(^1\) Patients with Fanconi’s anaemia may initially not be very ill, and show a good early response. They relapse when the drug is withdrawn and later become refractory. Patients with acquired disease may be very ill at first, but if they survive the early months the condition may improve and stabilise. Their long term survival is better than that of the Fanconi patients. To be effective the ‘non-virilising’ androgens are given in large doses and have definite virilising effects, not only on children’s physical, but also on their emotional and sexual development. Only 13 of 48 children (27%) in a recent European study survived beyond 10 months with androgens.\(^1\) In a multicentre American study with and without androgens 33 to 40% survived six months.\(^7\) For the past 20 years, survival has remained at about 30%.\(^5\)

For those who have a suitable donor the best results have been achieved with bone marrow transplantation with 70 to 90% surviving at six months.\(^7\) Nevertheless, of all diseases so treated, aplastic anaemia has proved to give the fewest survivals and the transplanted marrow may fail like the patient’s own. Fanconi’s anaemia patients may respond badly to preparation for bone marrow transplantation as they show increased sensitivity to x-irradiation and cyclophosphamide. For patients who lack a suitable donor, new treatments include immunosuppression with high dose bolus 6-methyl prednisolone or antilymphocyte globulin.\(^9\) Long term corticosteroid treatment cannot be recommended. Patients with aplastic anaemia already have neutropenia, and may also have lymphopenia, monocytopenia, and low serum immunoglobulins. Corticosteroid treatment only accentuates their predisposition to infection and does not alter the course of the disease.\(^7\)

**References**