Annotations

Red cell aplasia in children

Red cell aplasia in children is a condition characterised by failure of erythropoiesis, with normal production of white blood cells and platelets. The disorder is either acquired or constitutional (congenital or inherited). The constitutional disorder is usually permanent, while the acquired variety is often transient, and thereby differs from adult pure red cell aplasia. As the treatment and prognosis of a child with anaemia depend on the diagnosis, the distinctive feature of each disorder is described.

Constitutional red cell aplasia: Diamond-Blackfan anaemia

Children with anaemia without pancytopenia were first described in 1936, and again in 1938.^{1,2} More than 200 cases have now been reported and were reviewed recently.^{3,4} The diagnostic criteria include: (1) normochromic, often macrocytic anaemia without reticulocytopenia, developing early in childhood; (2) bone marrow with normal cellularity and usually a deficiency of red cell precursors (although these are occasionally normal or even increased); (3) normal or slightly decreased leucocyte counts; (4) normal or often increased platelet counts. The original term, 'congenital hypoplastic anaemia' was used because it was thought that the marrow was hypoplastic. The eponym, 'Diamond-Blackfan anaemia' is useful, since it justifiably indicates no specific aetiology of the disorder.

The diagnosis is made most commonly in infancy. 25% of reported infants were anaemic at birth, 65% by 6 months, and 90% by one year. Rare cases were diagnosed between 2 and 6 years of age. The male:female ratio is one. Most reported cases are Caucasian, but Blacks, Orientals, and Indians have been reported.

The inheritance of Diamond-Blackfan anaemia is not clear. Three-quarters of the reported cases were sporadic. Two families had parental consanguinity, and 13 families had more than one affected child. Thus autosomal recessive inheritance was suggested. However, 6 families were reported in which there was anaemia in one parent. In 3 additional families, the fathers had more than one affected child by unrelated wives. In a few families, one child had Diamond-Blackfan anaemia, while a sibling or a parent had transient anaemia (see below).

Mothers of affected children have reported an increased incidence of miscarriages or stillbirths. 10% of such infants were born after problem pregnancies, such as toxæmia, haemorrhage, and a variety of illnesses. Low birthweight occurred in 10%, divided equally between preterm infants and those who were small for gestational age.

Physical anomalies were reported in approximately 30% of cases (Table 1). The most common finding is short stature. Other abnormalities are microcephaly, cleft palate, abnormal eyes, web neck, and deformed thumbs. The anomalies resemble those seen in patients with Fanconi's pancytopenia, but are usually not as prominent in the children with Diamond-Blackfan anaemia. Abnormal thumbs were reported in 20 cases.⁵ 10 children had triphalangeal, and 7 had duplicated or bifid thumbs.

All patients are anaemic at the time of diagnosis. The anaemia is normochromic, but it is macrocytic in one-third. Reticulocyte counts are usually zero. White blood counts are normal or slightly decreased,

Table 1 *Physical findings in 229 patients with Diamond-Blackfan anaemia*

Abnormality	No. of cases
Height < 3rd centile	36
Microcephaly	9
Macrocephaly	2
Palate	
Cleft	12
High arched	3
Eyes	
Strabismus	6
Hypertelorism	8
Other (epicanthal folds, ptosis, blue sclerae, cataracts, microphthalmia)	14
Neck—short, and/or webbed	14
Thumbs	
Triphalangeal	10
Duplicated	7
Subluxed	2
Malformed	1
Mental retardation	9
Renal—caliectasis, partial horseshoe, double collecting system	7
Hypogonadism	5
Skeletal—scoliosis, Sprengel	3
Congenital heart disease	11
Ears—low set	7
Skin—café-au-lait spots	1
Toe syndactyly	2
At least one anomaly	60

Adapted from Alter⁴.

while platelet counts are normal or increased. The patients' erythrocytes have several characteristics which define them as 'fetal': macrocytosis, increased fetal Hb and fetal membrane antigen i, as well as fetal patterns of red cell enzymes.^{4,6} The bone marrow shows normal cellularity with erythroid hypoplasia in 90% of cases, while the rest have normal or hyperplastic erythroid development. Serum erythropoietin is increased, and most patients do not have serum inhibitors of erythropoiesis. Peripheral blood lymphocyte and bone marrow chromosomes are usually normal.

Cellular inhibition of erythropoiesis has been proposed but not confirmed as the pathophysiology of Diamond-Blackfan anaemia. Hoffman and co-workers found that the peripheral blood lymphocytes of 6 transfusion-dependent patients inhibited *in vitro* erythroid colony formation from normal bone marrow cells.⁷ Steinberg and co-workers also observed suppressor lymphocytes in 2 patients.⁸ However, Nathan and co-workers and Freedman and co-workers were unable to confirm this finding in a variety of patients.^{9,10,11} Those patients who had inhibitory cells in the study of Hoffman had received multiple transfusions, and had presumably been sensitised to antigens which happened to be present in the normal bone marrows which were used in the experiments.⁷ A similar problem has been reported in patients with acquired aplastic anaemia.¹²

The abnormality in Diamond-Blackfan anaemia appears to be in the erythroid stem cell. Null lymphocytes purified from peripheral blood contain erythroid progenitors, while T-lymphocytes produce soluble factors which stimulate *in vitro* colony formation from the null cell population.¹³ Nathan and co-workers mixed null and T-cells from normal subjects with those from patients with Diamond-Blackfan anaemia.¹⁴ T-cells from patients not only failed to inhibit, but actually stimulated erythroid colony formation from normal null cells. In contrast, null cells from patients failed to respond to normal T-cells. In other studies, *in vitro* erythroid colony formation from the bone marrow cells of patients with Diamond-Blackfan anaemia was decreased, and required unusually high levels of added erythropoietin. Thus the erythroid stem cell may have an abnormal response to the usual stimuli for erythropoiesis.

Patients with Diamond-Blackfan anaemia were initially treated by giving blood transfusions, and they died when these were stopped. Transfusions are still needed, at the time of diagnosis, and for about 20% of patients who do not respond to other forms of treatment. The current recommendation is that complete red cell typing be performed to reduce the possibility of sensitisation to red cell antigens. Frozen, washed, packed red cells should be used if

possible. Hb should be kept above 6 g/dl, with transfusions every 4 or 6 weeks. The main complication from multiple transfusions is iron overload; this may be controlled with chelating agents.¹⁵

Administration of corticosteroids leads to a response in approximately three-quarters of the patients. Initial treatment is with prednisone, 2 mg/kg per day (given in three or four doses). Reticulocytes appear between one and 3 weeks later. Daily treatment is continued until Hb reaches 10 g/dl. The corticosteroid dose is then tapered, and treatment is given on alternate days. Most patients require from 1 to 40 mg prednisone on the treatment days, given as a single dose in the morning. A few puzzling patients respond to corticosteroids initially, but then fail to maintain erythropoiesis on doses that are less than toxic. Occasionally, a combination of low-dose corticosteroids plus androgens has been useful. One patient was engrafted successfully with a bone marrow transplant, but unfortunately died from pulmonary complications caused by haemosiderosis.¹⁶ 20 to 30% of patients were reported to have spontaneous remissions from one to 16 years after the onset of their anaemia. The erythrocytes of most patients in 'remission', either corticosteroid-dependent or spontaneous, have fetal characteristics (see above), indicating that the patients are not cured of their underlying disease.

The reported mortality rate is approximately 15%, although it is undoubtedly higher. Most deaths were from complications of chronic transfusions and haemosiderosis—such as heart disease or pulmonary infections.

Recent reports have drawn attention to possible malignant complications. One patient developed hepatocellular carcinoma in a haemosiderotic liver.¹⁷ Two patients died with acute myelogenous leukaemia as adults. One had been in a spontaneous remission from ages 16 to 32, after several hundreds of transfusions in childhood.¹⁸ The other had received irradiation to long bones and thymus as a child, as well as many transfusions (L. K. Diamond, unpublished observations). One patient died with acute promyelocytic leukaemia; she had been transfusion-dependent, and had failed to respond to corticosteroids, cyclophosphamide, and androgens in the years before the leukaemia.¹⁹ One child did respond to treatment for acute lymphocytic leukaemia.²⁰ The interrelations of an abnormal erythroid stem cell, haemosiderosis, and immunosuppressive drugs, form a currently unresolved matter of concern.

Acquired red cell aplasia: transient erythroblastopenia of childhood

Temporary anaemia, reticulocytopenia, and marrow

erythroblastopenia have been reported in approximately 60 previously normal children (M. Link and B. P. Alter, unpublished observations). Transient reticulocytopenia is common in children with haemolytic disorders—such as hereditary spherocytosis or sickle cell disease—in whom anaemia is soon detected because of the short life span of the erythrocytes. The term 'transient erythroblastopenia of childhood' is restricted to those children who have no underlying haematological disease, and who recover. In Table 2 patients with this acquired and temporary anaemia are compared with those who have the constitutional permanent variety, Diamond-Blackfan anaemia. In the transient cases, a viral illness was usually noted 2 weeks to 2 months before diagnosis. All patients were between one month and 6 years of age, but 80% were between one and 4 years. The only unusual physical finding was pallor.

The blood shows anaemia, reticulocyte counts <1%, normal white blood counts, and normal or increased platelet counts (M. Link and B. P. Alter, unpublished observations). Red cell antibody tests are negative. Wang and Mentzer observed that patients with transient erythroblastopenia could be distinguished from those with Diamond-Blackfan anaemia because the erythrocytes of the former were adult in several features.⁶ This distinction is useful at the time of diagnosis. However, patients with transient erythroblastopenia do produce erythrocytes with fetal characteristics during their recovery phase. This temporary fetal erythropoiesis resembles the

chronic state of patients with Diamond-Blackfan anaemia (M. Link and B. P. Alter, unpublished observations). In transient erythroblastopenia, the bone marrow shows erythroid hypoplasia. Marrow culture *in vitro* did lead to normal erythroid colony formation in one study (B. J. Clarke *et al.*, unpublished observations); the erythroid cells which developed *in vitro* produced raised levels of fetal Hb. Recently, some patients with transient erythroblastopenia of childhood were found to have an IgG component in their sera which inhibits the growth of erythroid colonies in culture.²¹

Recovery is usually apparent within one month of diagnosis. Many children require a single transfusion because of the anaemia. Corticosteroids have been used in cases in which the diagnosis was thought to be Diamond-Blackfan anaemia. However, permanence of recovery after corticosteroids were stopped led to the correct diagnosis. The transient fetal erythropoiesis noted above is independent of the mode of therapy.

Transient erythroblastopenia probably occurs frequently, as reticulocytopenia often accompanies viral illnesses. The disorder is only detected if Hb drops to symptomatic levels, or if blood counts are obtained before the onset of anaemia. Many children recover without any specific treatment, and anaemia does not usually recur with subsequent viral infections.

Acquired red cell aplasia: adult pure red cell aplasia

Many adults and a few adolescents have been reported to have developed pure red cell aplasia. The adult diseases have been reviewed extensively by Krantz and co-workers, and should be considered in paediatric cases.^{22,23,24,25} Half the adults had an associated thymoma; the male:female ratio is 1:2 in those with, and 2:1 in those without this association. A few patients had malignancies. Children have been reported who developed red cell aplasia during treatment for leukaemia.²⁶ Many of the adults have had laboratory evidence of autoimmune disorders.

The anaemia is normochromic and normocytic, with reticulocytopenia. White blood counts and platelet counts are normal or decreased. Bone marrows show normal cellularity and erythroid hypoplasia. Autoimmune manifestations have included antibodies to red cells, smooth muscle, and intrinsic factor, as well as antinuclear antibody and paraproteins. Soluble inhibitors of erythropoiesis have been demonstrated in the IgG fraction from several patients. These antibodies have inhibited *in vitro* heme synthesis, and *in vitro* erythroid colony formation from normal marrow precursors. In some

Table 2 Comparison of childhood red cell aplasias

	Diamond-Blackfan anaemia	Transient erythroblastopenia of childhood
Number of reported cases	>200	60
Age at diagnosis	90%, <1 year	80%, 1 to 4 years
Aetiology	Constitutional	Acquired
Antecedent history	None	Viral illness
Physical examination	30%, abnormal (Table 1)	Normal
Laboratory		
Hb	2-4 g/dl	3-9 g/dl
White blood count	Normal	Normal
Platelet count		
>400 × 10 ⁹ /l	80%	100%
MCV increased		
At diagnosis	30%	0%
After recovery	100%	90%
During remission	100%	0%
Hb F increased		
At diagnosis	100%	0%
After recovery	100%	100%
During remission	85%	0%
i antigen		
At diagnosis	100%	0%
After recovery	100%	60%
During remission	90%	0%

Adapted from Alter⁴.

cases, the inhibitors were cytolytic to erythroblasts. A few patients had antibodies to erythropoietin.

The main treatment is transfusion. Thymectomy may be helpful in those with a thymoma. Splenectomy has had limited success. Chemotherapy has included corticosteroids, cyclophosphamide, azathioprine, and 6-mercaptopurine, and one, or a combination of these, has occasionally led to a remission. However, a guarded prognosis must be given to patients with the adult form of acquired red cell aplasia.

Conclusions

The form of red cell aplasia with the best prognosis is transient erythroblastopenia of childhood. Children acquire this anaemia rapidly, due to transient cessation of erythropoiesis. They also recover rapidly and apparently permanently. They exhibit temporary fetal erythropoiesis, similar to that seen in any type of stress erythropoiesis, but this disappears. Specific studies of erythropoiesis are incomplete because of the rapid course and rarity of patients. Although soluble or cellular inhibitors of erythropoiesis may be involved in some cases, the most likely aetiology is a failure of development of erythroid progenitors.

In adult pure red cell aplasia the disorder is long-lasting although there have been recoveries. Soluble inhibitors of various levels of erythropoiesis have been detected routinely. The erythroid progenitor cells themselves are apparently normal.

Constitutional red cell aplasia is apparently due to an abnormality in the erythroid stem cell itself. Most studies have failed to demonstrate soluble or cellular inhibitors of erythropoiesis. Treatment with corticosteroids leads to a partial correction of the erythropoietic defect, perhaps by improving the interaction of erythropoietin with erythropoietin-responsive stem cells. Further studies are required to define the abnormality more specifically. Meanwhile, patients with red cell aplasia of any except the most transient variety must be followed up because of the possibility of belated haematopoietic developments.

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