# Diamond Blackfan Anaemia (DBA) in Association with Polydactyly: Response to Antilymphocyte Globulin (ALG)

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## ABSTRACT

**An 8-month old Saudi Arabian boy presented with Diamond Blackfan Anaemia (DBA) and polydactyly. He required support with monthly red blood cell (RBC) transfusions. Although his bone marrow showed erythroblastopenia with giant pro-erythroblasts, examination of a later serum sample showed no evidence of B19 parvovirus DNA, and significant amounts of IgM and Igg anti-B19 antibodies. He showed no clinical improvement on a 3-month course of prednisone alone, subsequently followed by concommittant oxymethalone for 5 months. However, a 9 day course of daily infusion of anti lymphocyte globin (ALG) was followed by a significant improvement in haemoglobin. Although he briefly suffered a relapse about 9 months later, he recovered spontaneously and has been in complete remission since. We conclude that some patients with DBA may benefit from treatment with ALG.**

Diamond Blackfan Anaemia (DBA) or congenital pure cell aplasia (PRCA) is an infrequent disorder occurring in young children and characterised by severe erythroid hypoplasia; several congenital anomalies have been described in association[1]. The current thinking is that it may be due to a disorder of cellular immunity with a group of lymphocytes acting as erythroid suppressors[2-5]. In a majority of cases of PRCA, they respond to corticosteroids in regular or high doses[6] but some fail to do so and become dependent on regular blood transfusions. There are few reports of response to anti-lymphocyte globulin (ALG) in children either singly[7] or in combination with other agents such as Cyclophosphamide[8]. The purpose of this paper is to report a case of DBA responding to ALG alone, thus indirectly supporting the immune mediated aetiopathogenesis for the anaemia.

## THE CASE

An 8-month old Saudi male was referred to King Faisal Specialist Hospital and Research Centre (KFSH) from another hospital with a diagnosis of PRCA. He was the product of a full-term uncomplicated pregnancy and delivery. At birth he was found to have polydactyly of the right hand. He became anaemic at four weeks of age and required periodic packed red blood (PRBC) transfusions every month until he was referred to our hospital. The parents are distant relatives. The patient has four siblings, all alive and well. There is no family history of anaemia.

### Examination

Initial examination in February 1986, showed pallor and no jaundice, with 6.5 kg weight and 66 cm height, (both below the 5th percentile for age) and absence of hepatosplenomegaly. The ulnar border of the right hand showed the stump of the excised extra digit.

### Laboratory Data

Initial CBC showed Hb 43 g/L; Hct 0.132; RBC 1.7 x 10 E 12/L; MCV 77.5 fl; MCH 25.5 pg; MCHC 328 g/L; Retic 0.2%; WBC 16.5 x 10 E 9/L with segmented neutrophils (Segs) 30%, eosinophils (Eos) 2%,

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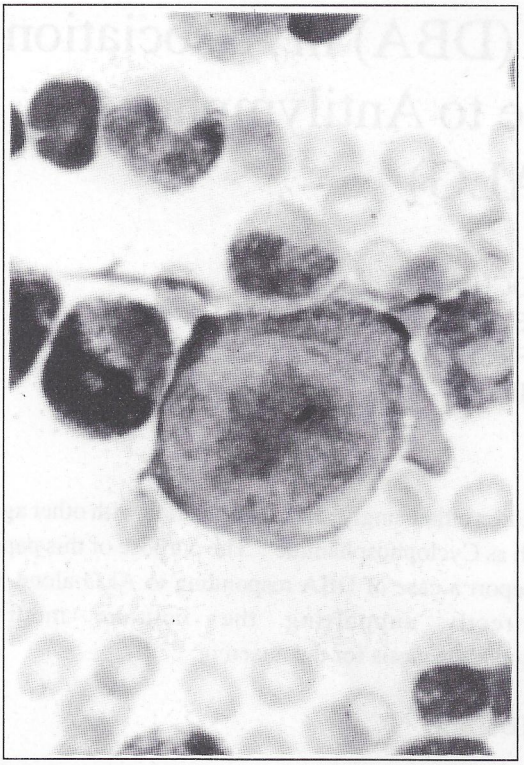

**Figure 1:** *Light photomicrograph of giant pro-erythroblasts in presentation bone marrow. Wright Geima stain.*
*Original magnification x 1000.*

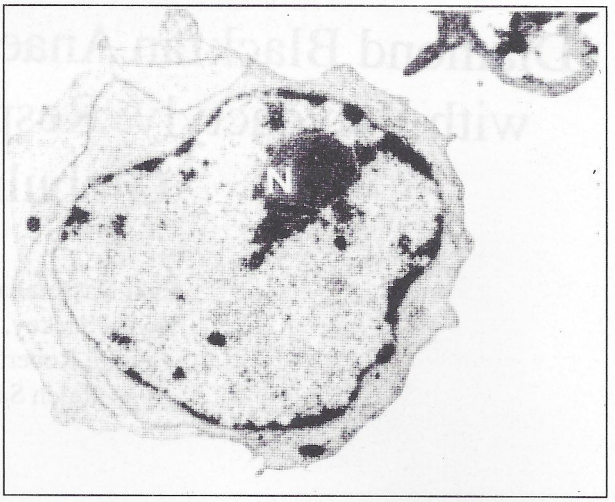


**Figure 2:** *Transmission electron photomicrograph of giant pro-erythroblasts in presentation bone marrow. The features are those of a primitive cell with few cytoplasmic organelles. A large, prominent nucleous (N) is seen in a nucleus formed of predominantly euchromatin. Lead citrate stain.*
*Original magnification x 5000.*

banophils (Basos) 2%, monocytes (Monos) 2%, lymphocytes (Lymphs) 64%, platelet count (PC) 1099 x 10E 9/L. Hb electrophoresis showed HbA1 97.7%, HbF 0.1% and HbA2 2.3%. Serum ferritin was 585 ug/L (Reference Range 134-626); serum folate 10.5 ug/L (RR 2.2-17.1) and Vitamin B12 279 ng/L (RR 165-920); western blot analysis for HIV 1 was negative; peripheral blood lymphocyte subsets were not done.

Bone marrow aspiration and biopsy showed a cellularity of 80-90% with active thrombopoiesis and granulopoiesis. Erythropoiesis was markedly reduced with mainly basophilic erythroblasts with a few giant pro-erythroblasts (Fig 1). There were no intermediate or late normoblasts. Transmission electron microscopy confirmed the presence of the giant pro-erythroblasts (Fig 2). Bone marrow chromosomes were normal.

At KFSH he was initially started on Prednisone alone at a dose of 2 mg/kg for 3 months, without response. Oxymetholone 2 mg/kg was then added but he still failed to respond, with a persistence of reticulocyte count less than 0.1%. Both corticosteroid and Oxymetholone were stopped in September 1986.

He was admitted to the Hospital in October 1986 for ALG. Prior to ALG his haematologic indices were as follows: Hb 55 g/L, Hct 0.155, retic 0.1%, RBC 1.9 x 10 E 12/L, MCV 81.4 fl, MCH 29.2 pg and MCHC 359 g/L; PC was 682 x 10 E9/L and WBC 10.3 x 10 E9/L with segs 40%, bands 1%, mono 3%, eos 4%, lymphs 49% and atypical lymphs 3%. He was given ALG by intravenous infusion 15 mg/kg over 12 hours daily for 9½ doses. The last dose was not complete because of difficulties with venous access. He was also given Benadryl 1 mg/kg/day and Prednisone 1 mg/kg/day for the total duration of treatment in order to reduce the immediate side effects of ALG. The only side effects were mild chills and fever on one occasion. He was discharged on Folic acid 1mg/day. He continued to require PRBC until 11th February 1987 when the reticulocyte count increased to 4.6%. He subsequently maintained a haemoglobin level greater than 100 g/L without transfusion until during an episode of acute febrile illness in September 1987, when his haemoglobin decreased precipitously to 77 g/L and he required a blood transfusion; the reticulocyte count during that period decreased to 0.1%.

No viral cultures or titres were obtained but the illness was presumed to have been due to a viral infection. The reticulocyte count recovered and he has not needed any further transfusion. He has been followed up for 64

months; his last CBC in January 1992 was Hb 140 g/L and reticulocyte count 0.6%. Serum taken at this time was kindly studied for B19 DNA and antibodies by Dr Neal S Young of the National Institutes of Health. No B19 DNA was demonstrable by dot blot hybridisation and antibody titres were IgM 1 and IgG 3.8 units.

## DISCUSSION

DBA is characterised by multiple congenital anomalies including short stature, thumb anomalies, webbed neck, cleft lip or palate, congenital heart disease, eye or ear anomalies, urinary tract anomalies, and mental retardation in association with pure red cell aplasia. The disease is usually first evident in early childhood typically before 2 years of age[3] but has been reported in the neonatal period[9].

Possible aetiologies that have been described include abnormal or absent stem cells, abnormal bone marrow micro-environment, or unresponsiveness to erythropoeitin[1]. Recently, there is accumulating evidence that cell mediated immunological mechanisms may play an important role in at least a subset of patients with PRCA[2-5].

Erythroid colony assays have been valuable in the study of DBA because they measure the proliferative activity of stem cell compartments related to red cell production BFU-E are primitive erythroid precursors and CFU-E are mature forms that differentiate into RBC in response to erythropoietin. Initial investigation in DBA showed that the marrow had decreased BFU-E and CFU-E and that peripheral blood had decreased BFU-E. Invitro studies showed that peripheral blood lymphocytes from patients with congenital PRCA suppress erythroid cell formation of normal human bone marrow in response to erythropoietin[5,10-13].

Most patients with DBA go into remission with corticosteroid treatment[6]; it is known that pharmacological doses of steroid cause lymphocytopenia, altered lymphocyte migration and protect against T-lymphocyte cell mediated cytotoxicity[5]. The clinical response of DBA to steroids, and other immunotherapies such as Danazol, Cyclophosphamide, Cyclosporin, plasmapheresis and splenectomy indirectly support an immune-mediated aetiopathogenesis[14-18]. Viruses are known to cause bone marrow aplasia by various mechanisms including alteration of cell mediated immune function in normal as well as in individuals with an underlying haematologic or immune defect. Parvovirus B19 has a particular tropism for erythroid progenitor cells[20] and may cause an acute, or less commonly, a chronic pure red cell aplasia[21].

The absence of B19 DNA and both IgG and IgM anti-B19 antibodies in this patient probably rules out the possibility that his anaemia was due to this virus (Fig 1 & 2). The transient relapse in this patient following an acute illness may have been due to alteration of the immunological balance, caused by a virus; unfortunately, no viral cultures or titres were obtained. There are few reports of response of childhood pure red cell aplasia to ALG with or without Cyclophosphamide[7,8]. Our case report adds to this limited information in the literature. In addition to which, this report has another feature of interest namely, the presence of polydactyly which has not been previously reported in association with DBA.

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