

## Diamond-Blackfan anaemia response to cyclosporin-A therapy six years after diagnosis

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**Abstract.** A boy with Diamond - Blackfan anaemia (DBA) diagnosed in infancy was started on cyclosporin A (CSA) therapy 10 mg/kg/day at 6 years of age after failure of prednisone therapy with increase of blood transfusion requirement and development of haemosiderosis. The patient exhibited a dramatic response to CSA with increase in reticulocyte count initially, followed by increase in haemoglobin level after splenectomy with minimal complications. Desferroxamine was started and the serum ferritin was reduced to <1000 mg/dl. He has remained transfusion independent for three years after starting CSA. Attempts to reduce the dose of CSA were followed by dramatic drop in his haemoglobin level and reticulocyte count. He is currently maintained on CSA and has no major side effects. CSA level was kept between 250-400 mcg/ml. His haemoglobin level ranged between 10-12 gm/dl and the reticulocyte count between 2-6 %. These results suggest that CSA therapy should be considered in patients with DBA anaemia, in whom steroid therapy has failed, even years after diagnosis.

**Key words:** Diamond-Blackfan anemia • Cyclosporin A therapy

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### INTRODUCTION

Diamond-Blackfan anaemia is a rare inherited congenital syndrome that is usually diagnosed in the first year of life and run a variable clinical course<sup>1</sup>. About 70% of patients respond to initial steroid therapy but they soon become resistant or require higher doses of steroids that can lead to severe toxicity. Ultimately patients fail to respond to steroids and become transfusion dependent<sup>2</sup>. Alternative forms of therapy include bone marrow transplantation (BMT), antithyocyte globulins (ATG) and CSA<sup>3,4</sup>. We treated a patient with complicated BDA using CSA that induced a long lasting remission and caused no major side effects.

### CASE REPORT

The patient was a Yemeni boy, referred to our center at the age of 6 years with a diagnosis of BDA. He was born in Yemen at term after a normal pregnancy and was diagnosed with congenital anaemia at the age of 9 months. Other siblings were normal and there was no family history of blood disease or malignancy. He was given a trial of steroids without effect and was then treated with monthly transfusions starting at the age of 18 months. His transfusion requirements had increased to every two weeks in the last few months. There were no symptoms of cardiac disease.

At presentation to our centre the patient looked sick, febrile, tachypnoec and very pale with bronze hy-

perpigmented skin colour. There was no jaundice. The temperature was 38°C, the heart rate was 130/min, the respiratory rate was 40/min and the blood pressure 105/65 mmHg. His weight was below the third percentile and height at the 10<sup>th</sup> percentile. There were no obvious congenital anomalies. On auscultation, the chest was full of crepitation. The liver and the spleen were palpable, 5 cm and 10 cm below the costal margins, respectively. The heart apex was laterally displaced at the sixth left intercostals space. A systolic thrill was felt at the apex. Auscultation revealed normal first heart sound, single second heart sound, no third heart sounds, a long systolic murmur at the apex, a diastolic murmur at the apex and a short systolic murmur in the aortic area. Other systems were normal. His haemoglobin was 4.3 g/dL and his reticulocyte count was 0.0%. His MCV was 85.2 fl, MCH 24 pg and MCHC 27 g/dL. Other haematological parameters were normal. The patient was treated with antibiotics and was given packed red cells transfusion. A bone marrow aspiration showed markedly reduced erythropoiesis, normal myelopoiesis and thrombopoiesis that confirmed the diagnosis of DBA. The iron stores of the bone marrow were high. Serum bilirubin was 8 mmol/L (normal values (N) ranged between 5-18 mmol/l), ALT 288 IU/l (N: 10-50 IU/l), AST 167 IU/l (N: 10-50 IU/l), and  $\gamma$ GT 116 IU/l (N: 8-61 IU/l). Hepatitis BsAg, and hepatitis BeAg were positive. Hepatitis BsAb, hepatitis C and HIV serology were negative. Blood glucose, serum urea and creatinine were normal. Serum ferritin was 5165 mcg/l. Echocardiogram showed left ventricular hypertrophy, mild aortic stenosis with post stenotic dilatation and a small ASD. The myocardial contractility was normal. The child showed clinical and biochemical evidence of severe haemosiderosis. He was given a trial of prednisone 2 mg/kg per day for four weeks along with desferroxamine chelation therapy (1 gr subcutaneously 5 days/week). There was no response to steroids and therefore he was started on CSA at 10 mg/kg/day. He had a rapid response with a reticulocyte count rising to 10.8% within one month. The prednisolone was discontinued after 2 months and the CSA was continued to maintain levels between 250-400 mcg/ml. Although the patient became transfusion independent, and the reticulocyte count had been increased, his haemoglobin did not rise above 8 g/l. This observation in addition to the increased transfusion requirements in the months preceding his arrival to our hospital were attributed to hypersplenism and therefore splenectomy and con-

comitant liver biopsy were performed. The liver biopsy confirmed haemosiderosis and mild fibrosis but there was no evidence of chronic hepatitis. Desferroxamine was continued and he maintained a good response to CSA for three years with a haemoglobin level between 10-12 gm/dl and reticulocyte of 2-5%. His haemoglobin and reticulocyte count fell only during minor infections and during two attempts to lower the CSA dose. The only complication of his CSA therapy was a mild degree of hirsutism. His serum ferritin has fallen to <1000 mg/dl and hepatomegaly regressed. He underwent cardiac surgery with correction of his aortic stenosis.

## DISCUSSION

DBA was first recognised as a distinct clinical entity in 1936 and given its current name and full description in 1938<sup>5,6</sup>. It is characterized by progressive normochromic usually macrocytic anaemia in infancy or early childhood; reticulocytopenia; normal cellularity of the bone marrow with markedly decreased or absent erythroid precursors; normal or slightly decreased white cell count and normal or slightly increased platelet count<sup>6-8</sup>. Congenital anomalies especially of the head and neck may be present in about 25% of cases that may also have short stature<sup>8</sup>. A report from UK Registry suggests an annual incidence of five cases per million live births<sup>9</sup>. The syndrome has been noted in several ethnic groups<sup>9,10</sup>. The majority of cases are sporadic, although familial cases with both dominant and recessive patterns of inheritance have occurred. In 1997 the chromosomal abnormality in DBA was mapped to chromosome 19 q13.2 and this observation lead to the cloning of a gene that encodes a ribosomal protein (RPS 19)<sup>11,12</sup>. Familial DBA chromosomal abnormality has also been mapped to chromosome 8p 23.3 p 22, however 20% of familial cases have neither the 19q or 8p abnormalities<sup>13</sup>. The pathogenesis of DBA is uncertain. The general consensus is that the defect is intrinsic to the erythroid progenitor cells characterized by an inability of precursor cells to undergo erythroid differentiation<sup>7</sup>. Some studies suggest a role of T-cell suppression of erythroid stem cells and hence the response to CSA and ATG therapy<sup>14</sup>.

Approximately 20-30% of children with DBA recover spontaneously<sup>8,15</sup>. Currently, patients diagnosed with DBA are treated with steroids with an initial response rate of 60-70% but subsequently 50% of patients of DBA fail<sup>2</sup>. CSA therapy is indicated in pa-

tients who are steroid refractory or who require high daily doses that causes toxicity<sup>3</sup>. Alternatively bone marrow transplantation is curative and has given an 83%, 2-year survival using an HLA identical sibling<sup>3</sup>. Fully matched sibling BMT is preferred to cyclosporin, a therapy that has been associated with increased risk of malignancy<sup>3,4</sup>.

The mechanism of action of CSA is through suppression of T lymphocytes, which are thought to suppress the bone marrow stem cells<sup>16</sup>. The response rate to CSA is up to 65%<sup>17,18</sup>. Patients usually need prolonged treatment and may stay on CSA for the rest of their life<sup>3</sup>. Several reports have been published about DBA patient who responded to CSA therapy. Out of the 22 reported patients: 4 (18.2%) had complete sustained response and 7 patients (31.8%) had transient response. The longest period of follow up of those patients was 15 months<sup>3,16,18,19</sup>. Alessandry et al reported a patient who has been followed up for 4 years and continued to be in remission<sup>3</sup>. Our patient however was followed up for 3 years and he is still in remission. This patient is interesting in the fact that despite a 6 year history with transfusion therapy the disease was responsive to CSA. The patient had transfusion acquired hepatitis B infection and severe iron overload but fortunately with no severe organ damage. He tolerated CSA therapy well and developed no major complications. As CSA has induced an initial marked reticulocyte response few days after starting treatment, it is probably that splenectomy has participated to the clinical improvement only by reducing hypersplenism and allowing Hb level to increase. Although the patient had severe haemosiderosis and deranged liver enzymes he tolerated CSA therapy very well. The patient, who has been reported here, is another example of long-term remission and sustained response to CSA but it is not clear whether this is permanent.

The patient treated by Alessandry et al has become CSA dependent [J. Davis personal communication December 2002]. It appears that our patient is CSA dependent as well. It is also likely that many patients with DBA will be CSA dependent.

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