Case Reports

Familial Diamond–Blackfan Anemia. Case Reports and a Review of the Related Literature

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Summary

We present the case of three sisters with Diamond–Blackfan anemia (DBA) from a consanguineous marriage. These sisters presented within the first 2 months of age with anemia without hepatosplenomegaly together with complete blood count and bone marrow pictures compatible with the diagnosis of DBA syndrome. They were given blood transfusions and then started on prednisolone 2mg/kg/day in divided doses, tapering the dose to a minimum to keep Hb around 90 g/l. DBA in these three sisters from a consanguineous marriage clearly illustrates the autosomal recessive mode of inheritance. The importance of early diagnosis and management with steroid is highlighted along with the need for consideration of other modalities of treatment in those cases not responding to steroid therapy.

Introduction

Diamond–Blackfan anemia (DBA) is a rare congenital abnormality of erythropoiesis that usually presents during infancy or early childhood and is characterized by normochromic macrocytic anemia, reticulocytopenia, normocellular marrow with specific deficiency of red cell precursors, normal or slightly decreased leukocyte counts, and normal or often decreased platelet counts. Associated phenotypic anomalies are found in about 50 per cent of the cases. This disorder occurs in a sporadic manner in most cases but can also be inherited as an autosomal recessive or dominant pattern. The male : female ratio is 1.1 : 1. Approximately 500 cases have been described worldwide. A variety of synonyms and eponyms have been used including congenital pure red cell aplasia, congenital hypoplastic anemia (CHA), and erythrogenesis imperfecta. We present here three sisters with this disease from early infancy and discuss the familial nature of the disease with a review of the relevant literature.

Case Reports

Case 1

An 11-year-old Kuwaiti girl was the firstborn to healthy consanguineous Kuwaiti parents by normal vaginal delivery at full term (FTND). Her birth-weight was 3.5 kg and there was no history of immediate post-natal problems. She presented at the age of 1 month with severe pallor and anemia without hepatosplenomegaly. The only dysmorphic feature was depressed nasal bridge and hypertelorism. Length and weight were at the 50th centile for age. There was no mucocutaneous bleeding or skeletal abnormalities. A complete blood count (CBC) picture at presentation revealed: Hb 25 g/l, mean corpuscular volume (MCV) 89 fl, reticulocytes (retics) 1 per cent, WBCs 6.3 $\times$ 10^9/l, polymorphonuclear leucocytes (poly) 34 per cent, lymph 63 per cent, monocytes (mono) 1 per cent, eosinophils (Eos) 2 per cent and platelet 202 $\times$ 10^9/l. Biochemical screening, G6PD and immunoglobulin electrophoresis were all normal. Direct Coombs’ test was negative. Ultrasound of the abdomen revealed normal echogenicity of liver, spleen, kidneys, and pancreas. Skeletal survey was normal. CBC and Hb electrophoresis of the parents were normal. She was given an urgent blood transfusion and was followed-up in our unit. She then became anemic again at the age of 4 months without hepatosplenomegaly. Bone marrow examination then revealed cellular marrow with absent erythropoiesis with normal granulopoiesis and megalakaryopoiesis without infiltration with abnormal cells. Hemoglobin electrophoresis...
revealed fetal Hb (Hbf) as 60 per cent. Based on the clinical picture and bone marrow findings, she was diagnosed as DBA. She was started on prednisolone 2mg/kg/day in divided doses. She showed a good response and tolerated the steroid therapy well. Steroids were gradually reduced to 2.5 mg every other day maintaining her Hb at 102 g/l. Her current weight and height are in the 50th centile for her age. Psychomotor development is normal and she is doing well at school.

Case 2
A 9-year-old girl is the sister of case 1. She is a product of FTND after an uneventful pregnancy with average birthweight. There was no history of neonatal problems. She was brought to us at the age of 1 month with severe pallor, inactivity, and hypertelorism without hepatosplenomegaly. Her weight and length were at the 50th centile for age. CBC showed: Hb 48 g/l, retics 1 per cent, MCV 101.4 fl, WBCs 6.0 × 10³/l, poly 23 per cent, lymph 75 per cent, eos 2 per cent, and platelet 400 × 10⁹/l. Biochemical screening, G6PD and immunoglobulin electrophoresis were normal. Direct Coombs’ test was negative. Because of DBA in her sister, this girl was also diagnosed with the same disease. She was given an urgent blood transfusion and was followed-up in our unit. At the age of 4 months she became anemic again and then had bone marrow examination, which revealed features consistent with DBA syndrome. Chromosomal analysis of the bone marrow revealed normal karyotype. Her Hbf was 63.8 per cent. She was then started on prednisolone 2 mg/kg/day in divided doses. She tolerated the steroid well and made a good response to the therapy. Steroid dose was tapered off gradually, the present dose being 2.5 mg twice weekly keeping her Hb around 103 g/l. Her current height and weight are at the 25th centile for age. Her school performance is very good indeed.

The parents then had a girl, now aged 7 years, and a boy, now aged 5 years, both being normal.

Case 3
A 10-month-old girl is the fifth child in the family. She is a product of FTND after an uneventful pregnancy with a birthweight of 4 kg. No neonatal problems were reported. She was seen in our unit at the age of 1 month with severe pallor and hypertelorism without hepatosplenomegaly. Her weight and height were at the 50th centile for age. CBC revealed Hb 58 g/l, retics less than 1 per cent, MCV 106 fl, WBCs 8.3 × 10³/l, poly 28 per cent, lymph 66 per cent, mono 1 per cent, eos 5 per cent, and platelet 408 × 10⁹/l. Biochemical screening, blood ammonia, lactate, and immunoglobulin electrophoresis were all normal. Direct Coombs’ test was negative. Virology screening for Epstein–Barr virus, parvovirus, cytomegalovirus, herpes simplex virus, hepatitis B and C virus, and HIV were negative. She was diagnosed as DBA in view of the family history. She was given a blood transfusion and followed-up. Bone marrow examination at the age of 2 months revealed cellular marrow with isolated red cell aplasia as in DBA. She was started at the age of 2 months on prednisolone 2 mg/kg/day in divided doses, gradually tapering the dose to keep her Hb around 100 g/l. She tolerated the steroid therapy very well without any side-effects. Her present dose of prednisolone is 2.5 mg every other day. Her psychomotor development is normal. Her present height and weight are above the 25th centile for age.

Discussion
DBA is a rare congenital hypoplastic anemia that usually presents early in infancy. Congenital anomalies, in particular of the head and upper limbs, are present in about a quarter of reported patients. The disease is characterized by moderate to severe macrocytic anemia, usually normal leukocytes and platelet count and normocellular bone marrow with erythroid hypoplasia. More than 500 cases have been described. The pathogenesis is likely to be heterogeneous, most cases (75 per cent) being sporadic. Familial cases with both dominant and recessive pattern of inheritance suggest that different molecular defects can result in the DBA phenotype. The incidence is 4–5 per million live births as per a retrospective study in the UK and the Netherlands. The incidence may be higher in areas known to have a higher rate of consanguineous marriage, such as middle-eastern countries. The occurrence of this disorder in three sisters within a consanguineous marriage of healthy Kuwaiti parents in this paper points to autosomal recessive pattern of inheritance. In the literature male:female ratio is 1:1.04 in contrast to our three patients who were all females. The anemia in DBA is usually diagnosed early in infancy but had been detected as late as 6 years of age. Ten per cent of cases are severely anemic at birth, 25 per cent by 1 month, 50 per cent by 2 months, 80 per cent by 6 months, and 90 per cent by 1 year of age. The three sisters in our study presented within 2 months of life. Physical signs and symptoms are usually related to the degree of anemia and to the congenital anomalies associated with this disorder. In approximately 30 per cent of affected children, DBA is associated with congenital malformations. The most common defects are cranio-facial dysmorphisms, including cleft palate, hypertelorism, neck anomalies (ptergium colli up to congenital elevation of the scapula and Klippel–Feil syndrome), thumb malformations (triphalangeal, bifid, accessory, absent, hypoplastic) and prenatal or postnatal growth failure. Various other anomalies are occasionally reported in association with DBA: urogenital malformations, congenital heart defects,
hypogonadism, or ear malformations. The three siblings in our study had average birthweight and their length and weight at presentation were on the 50th centile for age. The only dysmorphic feature is hypertelorism.

By definition, all DBA cases have normochromic macrocytic anemia. Reticulocytes are decreased or absent. Granulocytes are usually normal but may decrease with age to the degree of neutropenia. Platelet counts are usually normal but cases of slightly high or low counts have been described. Platelet function is usually normal. Fetal Hb is usually increased. Bone marrow has normal cellularity with erythroid hypoplasia or aplasia, the myeloid and megakaryocytic elements being normal. Our three cases fulfill all the criteria of a diagnosis of DBA and illustrate well autosomal recessive inheritance.

Treatment options in DBA includes corticosteroids, blood transfusion, iron chelation, immunosuppressive therapy (in selected cases), bone marrow transplant (BMT) and splenectomy (if hyper-splenism ensues), the cornerstone of treatment in DBA being steroid and blood transfusion. Steroid therapy has an overall response of 60 per cent and should be started as early as possible after diagnosis. Immunosuppressive therapy and recombinant growth factors had been tried in some cases. Allogeneic BMT is one modality of treatment that corrects the basic disorder completely and has to be considered for those who are refractory to steroid therapy and are blood transfusion-dependent if a HLA compatible donor is available.

The risk of malignancy is a recognized feature of DBA, predominantly hematological malignancy, including acute myelogenous leukemia and acute lymphocytic leukemia. There are fewer reports of DBA associated with solid tumors such as Hodgkin’s lymphoma, hepatocellular carcinoma, stomach carcinoma, osteogenic sarcoma, and malignant fibrous histiocytoma, but recently the number has been increasing. Our three cases with autosomal recessive mode of inheritance are responding well to steroid therapy but need long-term follow-up to see the course of the disease.

Conclusions

DBA is a pure red cell related disorder, with a good outcome with steroid therapy in most cases. Most of the cases are sporadic. The occurrence of the disease in the three sisters within the consanguineous marriage of Kuwaiti parents illustrates the mode of inheritance as autosomal recessive. Treatment with steroids (treatment of choice) has to be started as soon as possible after diagnosis. Transfusion-dependent cases (steroid-resistant cases) need good monitoring for the iron overload in order to start iron chelation and to consider other modalities of treatment including BMT.

References