Disease statistics

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The Life Saving Cord Blood Bank

DIAMOND BLACKFAN ANAEMIA

INTRODUCTION

- Diamond Blackfan anaemia (DBA) is one of a rare group of genetic disorders, known as the inherited bone marrow failure syndromes (IBMFS) [1].
- Diamond Blackfan anemia was first reported by Josephs in 1936 [2] and more completely described by Diamond and Blackfan in 1938 [3].
- It is also known as Blackfan-Diamond anemia, inherited pure red cell aplasia and as inherited erythroblastopenia.
- DBA causes low red blood cell counts (anemia), without substantially affecting the other blood components (the platelets and the white blood cells), which are usually normal.

1. Young NSAB. Inherited Bone Marrow Failure Syndromes: Introduction. Philadelphia: WB Saunders Company; 1994.
2. Josephs H. Anemia of infancy and early childhood. Medicine. 1936;15:307–451.
3. Diamond LK, Blackfan KD. Hypoplastic Anemia. American Journal of Diseases of Children.1938;56:464–467.

FEATURES OF DIAMOND-BLACKFAN ANEMIA

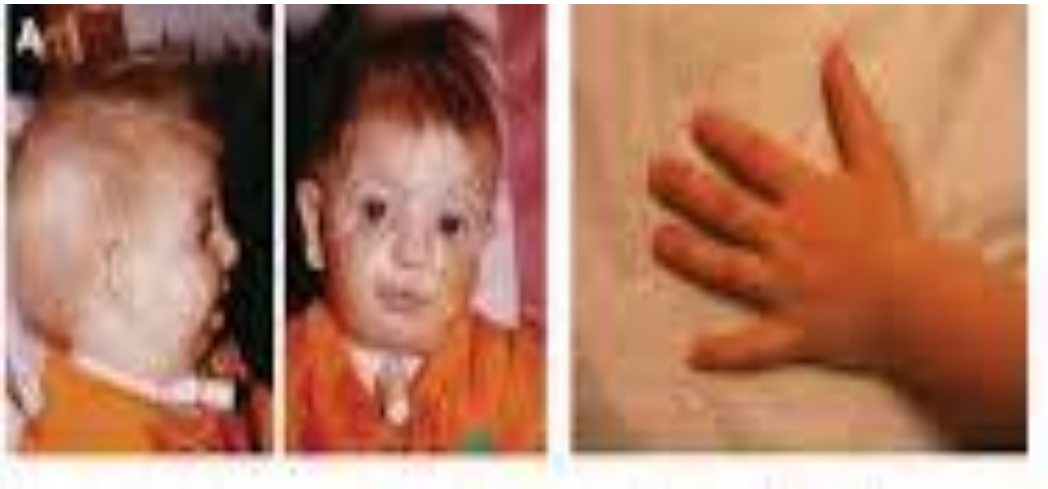
- Children with DBA appear to be normal, healthy infants at birth.

- Approximately 40% of the patients present with one or more congenital defects. Most of these abnormalities belong to the following categories:

1. Craniofacial dysmorphism including microcephaly, congenital cataract or glaucoma, strabismus, and a high-arched palate or cleft palate;
2. Thumb or upper limb abnormalities..
3. cardiac defects (ventricular and atrial septal defects)
4. Urogeniatal malformations (horseshoe kidneys, duplication of ureters, hypogonadism)
5. Tracheo-oesophageal fistula

DBA patients have a modest risk of developing leukemia and other malignancies.

- Certain facial characteristics often appear in children with DBA. It may consist of tow-colored hair (extremely blonde, almost white), a snub nose, wide-set eyes, and thick upper lip.
- In addition, the head can be small with almond-shaped eyes and a pointed chin.



EPIDEMIOLOGY AND INHERITANCE

- The incidence of DBA is estimated to range from 5 to 10 cases per million live births in Europe, with the lowest values in the UK and the highest in Northern Europe.[4, 5, 6]
- The vast majority of cases are sporadic; familiarity with either an autosomal dominant or, seldom, a recessive pattern of inheritance is reported in 10%-20% of patients.[7, 8]
- The male: female ratio is 1:1.04.

4. Ball SE, Mc Guckin CP, Jenkins G, GordonSmith C. Diamond-Blackfan anaemia in the U.K.: analysis of 80 cases from a 20 year birth cohort. Br J Haematol 1996; 4:645-53.

5. Willig T-N, Niemeyer CM, Leblanc T, TiemannC, Robert A, Budde J, *et al*. Identification of new prognosis factors from the clinical and epidemiologic analysis of a registry of 229 Diamond-Blackfan anemia patients. Pediatr Res 1999;46:553-61.

6. Willig TN, Ball S, Tchernia G. Current concepts and issues in Diamond-Blackfan anemia. Curr Opin Hematol 1998;5:109-15.

7. Young NS, Alter BP. Aplastic anemia: Acquired and Inherited. Philadelphia: WB Saunders Co. 1994. p. 361-83.

8.. Alter BP. The bone marrow failure syndrome.In: Nathan DG, Orkin SH (eds). Nathan and Oski's. Hematology of infancy and childhood. Philadelphia: WB Saunders Co. 1998. p. 237-335.

- Six children, four males and two females were diagnosed as Diamond-Blackfan anemia at *Division of Pediatric Hematology-Oncology, Department of Pediatrics, L.T.M.M. College and General Hospital, Sion, Mumbai, India in the year 2003*.

All had severe pallor at presentation, with mild hepatomegaly and just palpable spleen in one child. Thumb anomaly was present in one of them.[9]

- A total of 10 children (9 male and 1 female) were diagnosed at Department of Hematology, AIIMS, Delhi, India with DBA.[10]

9. Manglani M, Lokeshwar MR, Sharma R, Diamond-Blackfan anemia: report of 6 cases. Indian Pediatr.2003 Apr;40(4):355-8.
10. Avinash Kumar Singh, Nita Radhakrishna *et al.*, Diamond Blackfan Anemia: a Tertiary Care Center Experience, Mediterr J Hematol Infect Dis. 2013; 5(1): e2013039.

CLINICAL PRESENTATION

Physical abnormalities:

Short stature and congenital abnormalities, mainly involving the head, upper limbs, heart and urogenital system, occur in more than one-third of DBA patients.[11]

11. Willig TN, Gadza H, Sieff CA. DiamondBlackfan anemia. Curr Opin Hematol 2000; 7:85-94.

Hematologic features:

- All patients with DBA are, by definition, anemic.

Anemia is already evident at birth in 25% of cases; in almost all patients (95% in our series) presentation is in the first year of life.[7, 8] Red blood cells are usually macrocytic; reticulocyte counts are decreased or zero.

- The other hematologic lineages are not involved as a rule, though slightly abnormal low leukocyte and high platelet counts have been reported at diagnosis.[12,13]

- The activity of erythrocyte adenosine deaminase (eADA), a critical enzyme in the purine salvage pathway, is usually high in DBA patients.

12. Dianzani I, Garelli E, Ramenghi U. DiamondBlackfan anemia: a congenital defect in erythropoiesis. Haematologica 1996;81:56072.
13. Giri N, Kang E, Tisdale JF, Follman D, RiveraM, Schwartz GN, et al. Clinical and laboratory evidence for a trilineage haematopoietic defect in patients with refractory Diamond-Blackfan anaemia. Br J Haematol 2000;108:167-75.

DIAGNOSTIC CRITERIA

Diagnostic criteria for DBA (accepted by the DBA working group of the European Society for Paediatric Haematology and Immunology, ESPHI) [14]:

1. Normochromic, often macrocytic anemia developing in the first year of life
2. Profound reticulocytopenia
3. Normocellular bone marrow with selective deficiency of erythroid precursors
4. Normal or slightly reduced leukocyte count
5. Normal or slightly increased platelet count

14. Maria Francesca Campagnoli, Emanuela Garelli, *et al.,* Molecular basis of diamond-blackfan anemia: new findings from the italian registry and a review of the literature. Haematologica 2004; 89(4)::480-489.

- Typically, a diagnosis of DBA is made through a blood count and a bone marrow biopsy.

- About 20–25% of DBA patients may be identified with a genetic test for mutations in the RPS19 gene.

Treatment

The cornerstones of treatment remain-

1.Corticosteroids

2.Chronic red blood cell transfusions, and

3.Hematopoietic stem cell transplantation.

1. Corticosteroid Therapy (Prednisone, Prednisolone)-

- The goal of corticosteroid therapy is to take only what the person needs to keep the hemoglobin (a protein in red blood cells that carries oxygen to all of the organs in the body) at a healthy level (about 10 g/dL).
- If corticosteroids are going to work, the number of red blood cells usually increases in 2 to 4 weeks.
- Doctors usually prescribe a certain dose of corticosteroids for several weeks.
- Over time, the body might not respond to the corticosteroids and they will not work as well. If this happens, the doctor might increase the dose or suggest a different type of treatment such as blood transfusions or stem cell transplantation.
- More than 50% of patients respond to standard steroid therapy (prednisone 2 mg/kg/die orally), and some achieve long periods of remission.[7,15] However, many responders become steroid-dependent and may experience steroid-related complications.

http://www.cdc.gov/ncbddd/dba/cortiosteroid.html

15. Halperin DS, Freedman MH. Diamond-Blackfan anemia: etiology, pathophysiology, and treatment. Am J Pediatr Hematol Oncol 1989;11:380-94.

2. Blood Transfusion-

- Blood transfusions might be recommended just as needed when the hemoglobin is lower than normal, or as a chronic blood transfusion program.
- Chronic blood transfusions consists of scheduled blood transfusion every 3-6 weeks to maintain the hemoglobin level in a safe range.
- A DBA patient normally makes his or her own white blood cells and platelets, and therefore would only require transfusion of red blood cells.

http://www.cdc.gov/ncbddd/dba/transfusion.html

- Some reasons that a person with DBA might receive regularly scheduled blood transfusions are:

1. Other treatments (such as corticosteroids) have been unsuccessful
2. Side effects of other treatments are not tolerated
3. Anemia is very severe or causes complications.

- Negative side effects of blood transfusion therapy are uncommon but can include blood transfusion reactions, infections, the development of red blood cell antibodies, and iron overload in different organs of the body

Chelation Therapy-

- Iron overload can be prevented and treated with chelation therapy.
- Chelation therapy refers to using medication to remove excess metals, such as iron, from the body.
- Therefore, chelation therapy is a critical component to the health and well being of a DBA patient receiving chronic blood transfusions.

3. Stem cell therapy-

- Another type of treatment for DBA is to undergo a stem cell transplant.
- Stem cell transplants ("SCT") depending on the donor source are also known as

1. Bone marrow
2. Peripheral blood stem
3. Cord blood

http://www.cdc.gov/ncbddd/dba/stem.html

- For DBA patients, a stem cell transplant is intended to restore the marrow's ability to make red blood cells.
- Once the body starts producing red blood cells, the patient may experience a decrease in signs and symptoms of anemia, such as tiredness and paleness.
- Often times, stem cell transplant may result in a cure of DBA and, when successful, may often extend a person's life and improve the quality of life they are able to enjoy.
- The person will no longer require long-term steroid medicine or blood transfusions.

- Stem cell transplantation (SCT) has been explored as an alternative to chronic transfusions since 1976.[16]
- More than 70 DBA patients have undergone SCT so far[17,18,19] with an overall survival of about 85% at three years from sibling donors in more recent reports.[17,19]

16. August CS, King E, Githens JH, McIntosh K,Humbert JR, Greensheer, et al. Establishment of erythropoiesis following bone marrow transplantation in a patient with congenital hypoplastic anemia (DiamondBlackfan syndrome). Blood 1976; 48:4918.
17. Willig T-N, Niemeyer CM, Leblanc T, TiemannC, Robert A, Budde J, et al. Identification of new prognosis factors from the clinical and epidemiologic analysis of a registry of 229 Diamond-Blackfan anemia patients. Pediatr Res 1999;46:553-61.
18. Alter BP. Bone marrow transplant in Diamond-Blackfan anemia. Bone Marrow Transplant 1998;21:965-6.
19. Vlachos A, Federman N, Reyes-Haley C,Abramson J, Lipton JM. Hematopoietic stem cell transplantation for Diamond-Blackfan anemia: a report from the Diamond-Blackfan anemia registry. Bone Marrow Transplant 2001;27:381-6.

CASE STUDIES ON STEM CELL TREATMENT

1. Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative option for patients with Diamond Blackfan anaemia (DBA).

Fagioli F *et al*., reported the transplantation outcome of 30 Italian DBA patients referred to the Italian Association of Paediatric Haematology and Oncology Registry between 1990 and 2012.

This is one of the largest national registry cohorts of transplanted DBA patients.

A matched sibling donor was employed in 16 patients (53%), the remaining 14 patients (47%) were transplanted from matched unrelated donors.

Twenty-eight of the 30 patients engrafted.

The 5-year overall survival and transplant-related mortality was 74·4% and 25·6%, respectively.

Patients younger than 10 years as well as those transplanted after 2000 showed a significantly higher overall survival and a significantly lower risk of transplant-related mortality.

HSCT from a related or unrelated donor was a reasonable alternative to transfusion therapy in young and well chelated DBA patients. [20]

20. Fagioli F, Quarello P, Zecca M, *et al*. Haematopoietic stem cell transplantation for Diamond Blackfan anaemia: a report from the Italian Association of Paediatric Haematology and Oncology Registry. Br J Haematol 2014; 165:673.

2. A nine-year-old boy of north Indian descent with Diamond Blackfan anemia and Duchenne muscular dystrophy underwent successful allogeneic hematopoietic stem cell transplantation.

He is transfusion-independent, and his Duchenne muscular dystrophy has shown no clinical deterioration over the past 45 months.

The patient is 100% donor chimera in the hematopoietic system, and his muscle tissue has shown 8% to 10.4% cells of donor origin.

The patient's Diamond Blackfan anemia was cured by allogeneic hematopoietic stem cell transplantation.

The interesting clinical observation of a possible benefit in Duchenne muscular dystrophy cannot be ruled out. [21]

21. Velu Nair, Satyaranjan Das, *et al.,* Successful bone marrow transplantation in a patient with Diamond-Blackfan anemia with co-existing Duchenne muscular dystrophy: a case report. J Med Case Reports. 2011; 5: 216.

3. A 4-year-old boy with Diamond-Blackfan anaemia and a history of multiple transfusions underwent umbilical cord blood transplantation from his HLA-identical female sibling born by vaginal delivery at 38 weeks.

Regimen-related toxicity was not observed and successful engraftment occurred, including the erythroid series.

No evidence of acute or chronic GVHD has been observed for 14 months after transplantation.

This is the first case of successful umbilical cord blood transplantation to a patient with Diamond-Blackfan anaemia. [22]

22. Bonno M, Azuma E, Nakano T, *et al.* Successful hematopoietic reconstitution by transplantation of umbilical cord blood cells in a transfusion-dependent child with Diamond-Blackfan anemia. Bone Marrow Transplant 1997; 19:83.

4. Patients who underwent Umbilical Cord Blood Transplant (UCBT) for a diagnosis of DBA from 1996 to 2011 at Duke University Medical Center were eligible for retrospective analysis (n=6).

4 of 6 (67%) patients are alive and well, full donor chimeras, and free of transfusions.

None of the 4 surviving patients suffer from any major chronic medical problems.

UCBT can successfully be used for the treatment of DBA if otherwise suitable donors are not available. [23]

23. Alicia McFarren, MD, Kristin Page, *et al*., Unrelated Umbilical Cord Blood Transplant for Diamond-Blackfan Anemia. *Biology of Blood and Marrow Transplant* 20(2),Supplement: S177

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Thank you