A Case Report of Diamond-Blackfan Anaemia with RPS19 Mutation

Quazi Smita Haq1, Md. Maruf Al Hasan1, Muhammad Shahidul Islam Sikder1, Sazzad Zayed Chowdhury1, Masba Uddin Chowdhury1, Abu Jafar Mohammed Saleh1*

1Department of Haematology & Stem Cell Transplant, Evercare Hospitals, Dhaka, Bangladesh

ABSTRACT

Diamond Blackfan Anaemia (DBA) is a rare disorder which presents with anaemia in early childhood. This heterogenous disorder is mainly autosomal dominantly inherited. Significant proportions of the cases are associated with craniofacial anomalies and some cases may end up developing malignancy. The diagnosis is established by blood investigations, and bone marrow studies in which red cell precursors are reduced or absent. Screening for the mutations including those encoding for ribosomal proteins in the patient and the family members is confirmatory for diagnosis. Human Leukocyte Antigen (HLA) matched haemopoietic stem cell transplantation is the definitive treatment of choice. In other cases, corticosteroids have been tried. The haemoglobin level is maintained with packed red cell transfusion.

We are presenting here a male baby who had anaemia soon after birth and was brought to us at the age of 1 year 3 months. The diagnosis of DBA was made since the patient presented with anaemia and supportive biochemical and histological evidences. Genetic screening revealed mutation in ribosomal protein S19 (RPS19) gene in the baby.

Keywords: Diamond-Blackfan anaemia; DBA; Bone marrow failure; Rare disease; RPS19

Background

Diamond-Blackfan anaemia, one of a rare group of inherited bone marrow failure syndromes (IBMFSs), which is characterized by failure of erythropoiesis, presence of congenital anomalies, and predisposition to malignancy.1 It is considered as one of the ribosomopathies resulted from genetic mutations in one of 19 ribosomal proteins affecting ribosome synthesis.2,3

In more than 50% cases, the syndrome evolves from haploinsufficiency of either a small or large subunit associated ribosomal protein.4-10 Though exact pathogenesis by which ribosomal protein haploinsufficiency results in erythroid failure and other clinical manifestations, is not fully understood. The characteristic haematological features of DBA encompass a severe normochromic macrocytic anaemia, reticulocytopenia, gross erythroid hypoplasia in the bone marrow and an increased erythrocyte adenosine deaminase.11

The prevalence of DBA in Bangladesh is not currently known. Limitation in access to children's health care (tertiary) and knowledge around rare diseases is still a significant challenge in developing countries, which explains the low incidence of reported cases.
Case Report

Case Presentation

A one year three month old male baby born of a non-consanguineous marriage was brought to us with history of being severe paler at 3 month of age and receiving monthly blood transfusion since then. There is no history of jaundice. The developmental milestones were adequate. On examination he was severely pale but non-icteric.

The baby weighed 9.0 kg and head circumference 45 cm which was at the 50th percentile for age. There were no obvious craniofacial or skeletal abnormalities of note and other systems were normal (Fig 1).

The preliminary labs with normal ranges in brackets showed: Hb level -5.6 gm/dl (12.6±1.5 gm/dl), Haematocrit 16.5 (0.34±0.04 l/l), MCV 77.9 fl (78±6 fl),

---

**Figure 1:** Patient's face showing no craniofacial abnormality (A). Increased megakaryopoiesis and significant lymphocyte infiltration in bone marrow aspirate (B, C) and trephine (D).
Among the genes 25% patients carry a mutation in RPS 19 gene, which is located on chromosome 19q13.2. To date mutations in 19 ribosomal genes (RPS7, RPS10, RPS15A, RPS17, RPS19, RPS24, RPS26, RPS27, RPS28, RPS29, RPL5, RPL11, RPL15, RPL18, RPL26, RPL27, RPL31, RPL35, RPL35A) and 3 non ribosomal genes (GATA 1, TSR 2, EPO) have been involved in DBA. Patients with mutations in RPL11 are more often associated with physical malformations than RPS19 mutations. The mutations in RPL5 found to cause malformations in the heart and craniofacial region in contrast to mutations in RPS19. Hence, very minimal malformations in our subject prompted us to screen mutations in RPS19 gene.

The current criteria for establishing the diagnosis of DBA proposed by Vlachos et al, use clinical, histological, biochemical and genetic parameters. There are a number of obstacles using current proposed guidelines to make the diagnosis of DBA in Bangladesh. Mostly due to limited resources, tests and available health care services. Moreover, both genetic testing and eADA (erythrocyte ADA) are not available in Bangladesh and although bone marrow biopsies and histopathology are available, it is limited to a few larger tertiary hospitals.

DBA currently has no curative treatment option. Treatment options consist of, chronic RBC transfusions, corticosteroid therapy, and HSCT. Gene therapy, which is novel, comes up with a theoretical cure to DBA. Current guidelines suggest initially treatment with red cell transfusions until 1 year of age, when a trial of steroids should be carried out. Despite 70-80% of patients initially responding to corticosteroids, only half of them remain on corticosteroid doses low enough to minimize toxicity. Approximately 20% go into remission and the resting 40% remain transfusion dependent. Apart from corticosteroids, there are few case reports of remission or improvement in Hb level using leucine or metoclopramide.

Allogeneic HSCT is the treatment of choice that corrects the basic disorder completely and should be aforesought for those who are refractory to steroid therapy and are blood transfusion-dependent if an HLA compatible donor is available.

MCHC 33.7gm/dl (34±2 gm/dl); Absolute reticulocyte count 5.1x10⁹/ L (20-60x10⁹/L). His white cell count was 11.82 x 10⁹/L (11±5 x10⁹/L) and platelet count 401x10⁹/L (200-550x10⁹/L). Hb electrophoresis was normal.

As he presented with long duration of history without any feature of infection, bone marrow aspiration and biopsy were done. Bone marrow biopsy showed reactive features with markedly increased megalakaryopoesis and significant lymphocyte infiltration (Fig 1). Red cell precursors were grossly reduced. Flow cytometry demonstrated the infiltrate to consist of T cells, mature B cells. Chromosomal analysis of the bone marrow revealed normal karyotype. Genetic analysis was carried out in abroad. Targeted gene sequencing confirmed a heterozygous 5’ splice site variation in intron 3 of the RPS19 gene.

We made a diagnosis of classical DBA, since the baby presented with infantile anaemia, normal white cell count and platelet counts, reticulocytopenia, paucity of red cell precursors in bone marrow, supporting criteria of gene mutation in RPS19 gene. There was no evidence of any other bone marrow failure syndrome. He was started on prednisolone 2 mg/kg /day in divided doses. He tolerated the steroid well and made a good response to therapy. Steroid dose was tapered off gradually; the present dose is 1.5 mg per day.

**Discussion**

DBA is one of the rare causes of aplastic anaemia and the principle differential diagnosis of anaemia due to decreased RBC production includes TEC (Transient reythroblastopenia of childhood), infections and other genetic causes of bone marrow failure. These are usually associated with additional cytopenias. Other acquired causes include aplasia associated with viral infections, drugs, autoimmune conditions, malignancies, and, rarely in adults, a thymoma needs to be considered. Congenital anomalies involve craniofacial region, eyes, neck, thumb, urogenital tract, heart, and musculoskeletal structures. Some patients may present with short stature, growth retardation and learning difficulties. Among the genes 25% patients carry a mutation in RPS 19 gene, which is located on chromosome 19q13.2. To date mutations in 19 ribosomal genes (RPS7, RPS10, RPS15A, RPS17, RPS19, RPS24, RPS26, RPS27, RPS28, RPS29, RPL5, RPL11, RPL15, RPL18, RPL26, RPL27, RPL31, RPL35, RPL35A) and 3 non ribosomal genes (GATA 1, TSR 2, EPO) have been involved in DBA. Patients with mutations in RPL11 are more often associated with physical malformations than RPS19 mutations. The mutations in RPL5 found to cause malformations in the heart and craniofacial region in contrast to mutations in RPS19. Hence, very minimal malformations in our subject prompted us to screen mutations in RPS19 gene.

The current criteria for establishing the diagnosis of DBA proposed by Vlachos et al, use clinical, histological, biochemical and genetic parameters. There are a number of obstacles using current proposed guidelines to make the diagnosis of DBA in Bangladesh. Mostly due to limited resources, tests and available health care services. Moreover, both genetic testing and eADA (erythrocyte ADA) are not available in Bangladesh and although bone marrow biopsies and histopathology are available, it is limited to a few larger tertiary hospitals.

DBA currently has no curative treatment option. Treatment options consist of, chronic RBC transfusions, corticosteroid therapy, and HSCT. Gene therapy, which is novel, comes up with a theoretical cure to DBA. Current guidelines suggest initially treatment with red cell transfusions until 1 year of age, when a trial of steroids should be carried out. Despite 70-80% of patients initially responding to corticosteroids, only half of them remain on corticosteroid doses low enough to minimize toxicity. Approximately 20% go into remission and the resting 40% remain transfusion dependent. Apart from corticosteroids, there are few case reports of remission or improvement in Hb level using leucine or metoclopramide.

Allogeneic HSCT is the treatment of choice that corrects the basic disorder completely and should be aforesought for those who are refractory to steroid therapy and are blood transfusion-dependent if an HLA compatible donor is available.
Conclusion

To the best of our knowledge though DBA have been reported in Bangladesh, no genetic studies have been done in those cases. This is the first classical case of DBA with RPS 19 mutation confirmed by genetic study in Bangladesh. Our case is responding well to steroid therapy but need long term follow-up to see the course of disease.

References


