Case Report

Diamond Blackfan Anaemia with Hypothyroidism and CNS Malformations

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Abstract

Diamond Black fan Anemia (DBA) is a congenital erythroid aplasia that usually presents in infancy. The DBA patients have low red blood cell count (Anaemia). The rest of their blood cells (Platelets & WBCs) are normal. We present a 14 month old male child who presented with severe anaemia. The patient was transfusion dependent since 4 months of age. Clinical examination revealed delayed mile stones and a couple of congenital deformities. Haematological parameters showed elevated foetal haemoglobin level (Hb F – 11.8%) and elevated serum TSH (thyroid stimulating hormone) level. Peripheral blood picture showed gross microcytic hypochromic red blood cells and absence of reticulocytes with normal levels of leucocytes and platelets. A bone marrow showed gross suppression of Erythroid series with M:E ratio of 30:1. Some large pronormoblasts were found. Family history was not significant. Compiling the clinical features, haematological parameters, PS and bone marrow findings, a diagnosis of DBA was given.

Keywords

DBA, Hypothyroidism, CNS malformation

Introduction

DBA was first recognized at Boston Children's Hospital by two physicians after whom the disease was named. It's a very rare anaemia, affecting five to seven children per million. It is a potentially life threatening condition that causes severe anaemia and requires on going blood transfusions. It is usually associated with birth defects and abnormal features. Low birth weight and generalized growth delay are usually observed. Diagnosis of DBA is made on the basis of blood count and bone marrow study. Patients have anaemia, low reticulocyte count, diminished erythroid precursors in bone marrow with increase in number of pronormoblasts. Congenital anomalies, macrocytosis, elevated fetal haemoglobin and elevated deaminase levels support the diagnosis of DBA. About 10% - 25% patients may be identified with a genetic test for mutations in the RPS 19 Gene. Approx. 20% - 25% cases have a family history of the disease and most pedigrees suggest an autosomal dominant mode of inheritance.

The disease is characterized by genetic heterogeneity, with current evidence supporting the existence of at least three genes mutated in DBA. The phenotype of DBA patients suggests a haematological stem cell defect, specifically

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affecting the erythroid progenitor population. This is difficult to reconcile with the known function of the single known DBA gene. The RPS19 protein is involved in the production of ribosomes. As such loss of RPS 19 function would be predicated to affect translation and protein biosynthesis and have a much broader impact. Disease future may be related to the nature of RPS19 mutations. The disease is characterized by dominant inheritance and therefore arises due to a partial loss of RPS 19 protein function. It is possible that erythroid progenitors are acutely sensitized to this decreased function.

Case History

A 14month old child presented with severe anaemia & was transfusion dependent since 4 months of age. A detailed clinical examination revealed some congenital anomalies (**Fg. 1**). There was defect in Rt. eye with lagophthalmous, flattening of nasal bridge and widely spaced ears. MRI of

Fig. 1
14 month male child with lagopthalmous and flattened nasal bridge

brain showed early temporal shrinkage and hypoplastic corpus callosum. Haematological parameters showed a hypothyroid state with elevated serum TSH level. Fetal haemoglobin level was raised (11.8%), HbA-76.8% and HbA_2 - 4.9%. Coagulation studies like BT, CT, PT and

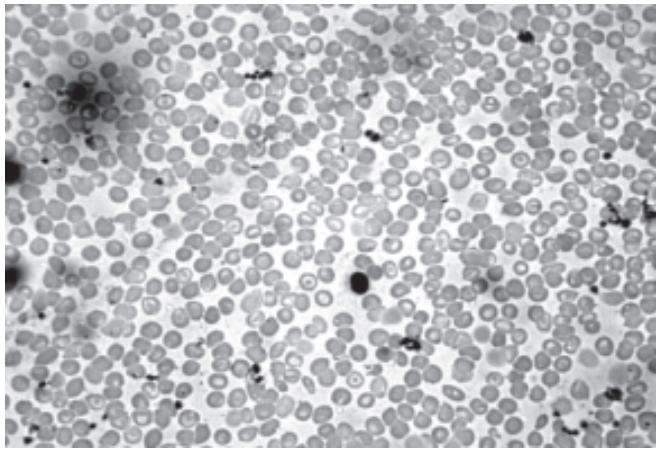

Fig. 2
Peripheral semar showing microcytic hypochromic anaemia

aPTT were within normal range. Peripheral smear showed gross microcytic hypochromic anaemia (**Fig. 2**) with total leucocyte count and platelet count within normal limit. Haemoglobin level was 9.2 gm %. For further evaluation of the cause of anaemia, a bone marrow aspiration study was done. The marrow was slightly hypocellular but with

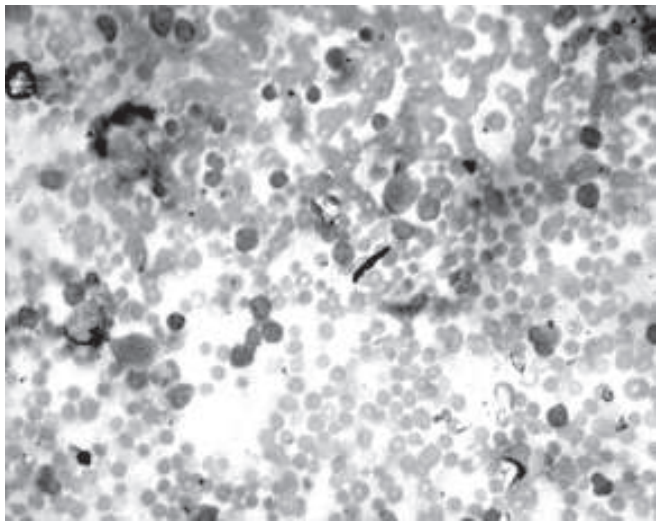

Fig. 3
Bone marrow showing M:E ratio 30:1

gross depression of erythroid precursors with a M.E. ratio of 30:1 (**Fig. 3**). Some large pronormoblasts were seen which were predominant among erythroid series (**Fig. 4**). Clinical findings, haematological parameters, peripheral smear findings and bone marrow picture compiled together led us to diagnose DBA.

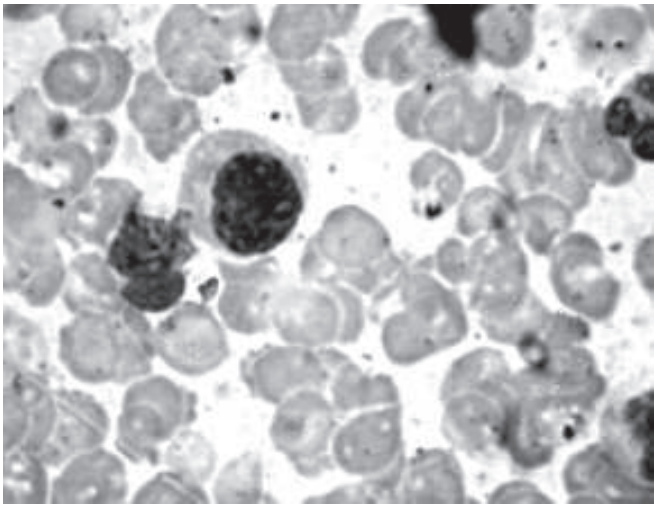

Fig. 4
Bone marrow showing large pronormoblasts

Discussion

DBA is a rare, pure red cell aplasia, predominantly of infancy and childhood, resulting from an intrinsic erythroid progenitor defect. DBF patients have primarily low red cell counts (Anaemia) with a normal platelet and white cells as found in our case. Our closest differential diagnosis was Transient Erythroblastopenia of Childhood (TEC), which is usually diagnosed in 2nd to 3rd year of life as compared to DBF which manifests in 1st year of life2. TEC has a history of preceding viral illness with no congenital anomaly2. Fetal haemoglobin is normal in TEC and the patient recovers spontaneously within 1 to 2 months. But in our case, Fb H was high and the patient was transfusion dependent since 4th month of life, and was diagnosed in 14th month of life. Fanconi's Anaemia patients also have similar presentations but the pattern of bone marrow failure is different from DBF. FA patients present with aplastic anaemia showing absence of all 3 cell types in bone marrow. But in DBF there is only red cell aplasia with few large pronormoblasts as was present in our case. FA can be readily diagnosed by chromosomal breakage test where as DBF patients show genetic mutations in only 25% to 30% cases.

Other causes of inherited bone marrow failure syndromes/Pure red cell aplasia like Schwamann– Diamond Syndrome and Pearson syndrome, parvovirus B-19 & HIV infections were excluded. So a history of transfusion dependent anemia with red cell aplasia, presence of few pronormoblasts, elevated fetal haemoglobin and increased red cell ADA level helped us to clinch the diagnosis of DFA.

DBA is a rare congenital hypoplastic anaemia that usually presents early in infancy. Congenital anomalies in particular of the head, face and upper limbs are present in 25% of reported patients[3] and our case also showed rare congenital anomaly of face and head. Craniofacial anomalies are the most common, representing 50% of anomalies reported to the North American DBA registry, with hypertelorism and flat nasal bridge contributing to the classic DBA facies described by Cathie (1950)[4]. Our case showed flat nasal bridge and lagopthalmous, prominent forehead and widely spaced ears. Thumb anomaly is described in 9-19% cases[5], but was absent in our case. Renal, cardiac, musculoskeletal, neuromotor and CNS anomalies have been described in 7% of patients in the UK, France & Italy. However, in North American DBA Registry the prevalence is higher (15%). In our case there was hypothyroidism but no renal, cardiac or musculoskeletal anomaly. Growth retardation is described in about 30% of children[6] as well as in our case. It must be noted that stature is difficult to evaluate in the context of severe anaemia, iron overload and chronic corticosteroid use.

MRI of brain in our case showed early temporal lobe shrinkage and hypoplastic corpus callosum. Temporal lobe shrinkage association with DBA has not been reported previously. However, corpus callosum defect in association with DBA[7] has been reported previously.

Our case, a rare association of hypothyroidism and temporal lobe shrinkage and hypoplastic corpus callosum with DBA calls the need for increase awareness about the association of CNS malformations and endocrine malfunctions in DBA patients. It has also expanded the list of congenital anomalies associated with DBA. It implicates a detailed evaluation of DBA patients like thorough history, physical examination, blood and bone marrow studies, detailed haematological studies with hormones & enzymes level, MRI and ECG to increase their standard of health and prevent complications like risks for malignancy and infection.

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