Diamond Blackfan Anaemia

Article · May 2024

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Diamond Blackfan Anaemia

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Abstract

DBA is a rare genetic blood disorder that affects the production of red blood cells and can cause a range of symptoms. DBA is a rare congenital disease, with an incidence of 7 cases per million live births. Diagnosis is established at a median age of 2 to 3 months, with 95% of DBA cases diagnosed before 2 years of age and 99% before 5 years of age. Diamond Blackfan anaemia (DBA) occurs as a result of genetic mutation, resulting in defect in the ribosomal RNA (rRNA) maturation as a consequence of a heterozygous mutation in 1 of the 20 ribosomal protein genes. Early diagnosis and treatment are important for managing the condition and preventing complications. Ongoing research is needed to better understand the molecular pathogenesis of DBA and to develop more effective treatments for this rare disorder.

Keywords: *Diamond Blackfan Anaemia*

Introduction

Diamond-Blackfan anaemia (DBA) is a rare congenital intrinsic erythroid hypoplasia, identified as the first human ribosomopathy in 2005 (1). It is categorized as a congenital hypoplastic anaemia presenting during infancy with normochromic-macrocytic anaemia, reticulocytopenia, and low numbers of erythroid precursors in the bone marrow (2). The majority of DBA patients carry haploinsufficient mutations in one of several ribosomal genes (3). To date mutations in 20 ribosomal protein (RP) genes associated with DBA have been identified that leads to defective ribosomal RNA (rRNA) maturation, the signature feature of classical DBA. The definition of DBA has become somewhat problematic due to some patients exhibiting erythroblastopenia resulting

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from non-RP mutated genes (*GATA1, EPO, and ADA2*). Moreover, some patients without any history of anaemia exhibit a pathogenous mutation in a ribosomal protein (RP) gene associated with a malformative syndrome or preleukemic state (1). Classically individuals with this condition present with severe anaemia in early infancy, often in association with physical anomalies and short stature (4). Diamond Blackfan anaemia is a rare genetic disorder, amongst the inherited bone marrow failure syndromes (IBMFS) (5) that primarily affects the ability of the bone marrow to produce red blood cells. DBA can thus be defined as an intrinsic defect in erythropoiesis due to defective ribosome processing (6). These disorders have in common pro-apoptotic haematopoiesis, bone marrow failure, birth defects (7) and in the majority a predisposition to cancer (8). Diamond-Blackfan anaemia has previously been known as:Congenital pure red cell aplasia, Congenital erythroid hypoplastic aplasia, Blackfan-Diamond syndrome (BDS), Aase syndrome, Aase-Smith syndrome II, Blackfan Diamond anaemia (BDA), Blackfan Diamond disease, Inherited erythroblastopenia, Chronic congenital agenerative anaemia, Chronic idiopathic erythroblastopenia with aplastic anaemia or Erythrogenesis imperfecta (9)

Brief history and discovery of diamond Blackfan anaemia

Hugh W. Josephs first recognised the syndrome in 1936 as "anaemia of early infancy", but the physician Louis K. Diamond and Kenneth Blackfan, first documented congenital hypoplastic anaemia in 1938 making it recognized as a specific clinical entity, and were credited with giving it its name (3). In the year 1961, Diamond and colleagues presented longitudinal data on 30 patients and noted an association with skeletal abnormalities (10). Diamond Blackfan anaemia (DBA) moved into the scientific limelight after the unexpected identification of RPS19, the gene encoding ribosomal protein S19 (rpS19) (4). In 1999, a mutation in ribosomal protein S19 (RPS19), one of the proteins in the 40S small ribosomal subunit, was identified as the first causal genetic lesions for DBA that explained 25% of case subjects. Through the use of whole-exome sequencing (WES) and copy number variant (CNV) assays, putatively causal haploinsufficient variants have been identified in 19 of the 79 ribosomal protein (RP) genes RPS19, RPL5, RPS26, RPL11, RPL35A, RPS10, RPS2, RPS17, RPS7, RPL26, RPL15, RPS29, RPS28, RPL31, RPS27, RPL27, RPL35, RPL18, RPS15, making DBA one of the best genetically defined congenital disorders (11). Due to this discovery, it has been established that DBA is a condition of ribosomal biogenesis or function due to the mutations affecting additional ribosomal protein genes. This is supported by the revelation of RPS14 haploinsufficiency which causes the macrocytic anaemia linked to the 5q syndrome (4). In 2012, through the use of whole-exome sequencing (WES), mutations in GATA1, a hematopoietic master transcription factor that is both responsible for proper erythropoiesis and sufficient to reprogram alternative hematopoietic lineages to an erythroid fate, was identified as the first non-RP mutations in DBA. Further studies on GATA1 and other novel genes mutated in DBA, have provided new insights into the pathogenesis of this disorder, suggesting that DBA results from impaired translation of key erythroid transcripts, in early hematopoietic progenitors which ultimately impairs erythroid lineage commitment (11).

Epidemiology

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DBA is a rare congenital disease, with an incidence of 7 cases per million live births. Diagnosis is established at a median age of 2 to 3 months, with 95% of DBA cases diagnosed before 2 years of age and 99% before 5 years of age. DBA has also been diagnosed at birth in 13% to 16% of cases. However, progress in molecular diagnosis is enabling DBA diagnosis in more patients with unusual clinical presentation, such as unexplained anaemia during foetal life or hydrops foetalis, and adult patients with mild anaemia (1). In the United Kingdom, a retrospective study on 80 cases reported an estimated incidence of five DBA cases per one million live births. There is no known gender predilection. Males and females are equally affected, although patients with variants in large (*RPL)* versus small **(***RPS*) ribosomal protein (RP) genes are more likely to be female. There is no apparent difference in prevalence among ethnic groups (12).

DBA in Africans is generally unknown due to the lack of existing national registries and a dearth of skilled specialists. A study conducted by Ulasi and colleagues reported for the first time two cases of Diamond Blackfan anaemia in Nigerian toddlers with a chronic history of recurrent severe anaemia since birth (13).

Etiology and Genetics of Diamond Blackfan Anaemia

Diamond Blackfan anaemia (DBA) occurs as a result of genetic mutation, resulting in defect in the ribosomal RNA (rRNA) maturation as a consequence of a heterozygous mutation in 1 of the 20 ribosomal protein genes (14). All identified mutations are heterozygous, and homozygosity is considered to be lethal. In about 60% to 70% cases of DBA ribosomal gene mutations are more common, 30 to 35% of cases remain genetically indeterminate. It involves the gene that codes for both small and large ribosomal protein units, which include, but not limited to, RPL5, RPL11, RPS 7, RPS 17, RPS 24, RPS 10, RPS 19, and RPS 26. In some families, mutations in RPL3, RPL7, RPL14, RPL19, RPL26, RPL36, RPL23A, RPL35, RPS 15, RPS 8, RPS27A, RPL35, and RPL18 gene has occurred (1). These genes provide instructions for making several of the approximately 80 different ribosomal proteins, which are components of cellular structures called ribosomes which process the cell's genetic instructions to create proteins. The most commonly mutated gene is ribosomal protein (RP) S19 which is seen in approximately 25% of patients (15), with various types of mutations present in more than 50% of RPS mutations. RPS19 protein plays an important role in 18S rRNA maturation and 40S synthesis in human cells and mutations associated with RPS19 leads to decreased expression of RPS19 protein (known as haploinsufficiency) (16). Most mutations identified in *RPS19* gene are missense, whereas nonsense mutations, small deletions or insertions, and splice site mutations are found in *RPL5* and *RPL11 (1)*. Large deletions have been found in ~20% of DBA cases, mostly in *RPS17*, *RPS19*, *RPL5*, *RPS26*, *RPL11*, *RPL35a*, and *RPS24*, using different techniques (quantitative polymerase chain reaction, multiplex ligation-dependent probe amplification, comparative genomic hybridization). However, in newer studies research has also noted mutations of transcription factor GATA1 (16).

The mutant genes that encode ribosomal proteins (RP) are responsible for the defect in ribosomal biogenesis in most DBA patients, directly affecting the process of erythropoiesis. Erythroid failure in DBA patients is characterized by a significant reduction of erythroid precursors/progenitors in bone marrow, specifically, a blockade between the burst-forming

unit-erythroid (BFU-E) and colony-forming unit-erythroid (CFU-E) stages or between the erythropoietin-independent and erythropoietin-dependent stages of erythroid development. As a consequence, erythrocyte maturation is arrested leading to a toxic elevation of heme (17).

Table 1: Genes involved in DBA and DBA-like syndrome from the most to least frequently mutated: reported cases and incidences (6)

Mutated gene	Incidence in DBA population
Genes involved in DBA	
RSP19	25%-30%
RPL5	7%-12%
RPS26	6.6%-9%
RPL11	5%-7%
RPL35a	2%-3%
RPS10	1%-3%
RPS24	2.4%-3%
RPS17	1%-3%
RP28	2 cases

Inheritance patterns

Approximately 40 – 45% of DBA cases are hereditary which are inherited with autosomal dominant inheritance pattern which mean that a single copy of altered gene in each cell is responsible for the disorder whereas the remaining 55 – 60% of the DBA patients are sporadic, i.e. resulted from new aberrations in the gene which occur in people who have no history of this disorder in their family (18). Even though autosomal dominant inheritance is the frequently observed pattern of inheritance, autosomal recessive inheritance, which is defined as the presence of DBA siblings from unaffected consanguineous parents, is observed with a lesser frequency. DBA classically presents at 2 - 3 months of age with only 25% of affected offsprings been anaemic at birth and occasionally with hydrops (18).

Pathophysiology of Diamond Blackfan anaemia and complications of diamond blackfan anaemia

Pathophysiology of Diamond Blackfan anaemia

Molecular mechanisms underlying the causal consequence between RP haploinsufficiency and anaemia have not yet been clearly elucidated. A generally documented pathogenetic hypothesis implies that a defective ribosome biosynthesis leads to apoptosis in erythroid progenitors which in turn is leading to erythroid failure. This mechanism has been named ‘‘ribosomal stress’’, and there are indications that it may be signalled through p53. All genes identified to be mutated in DBA encode ribosomal proteins which are involved in either the small (RPS) or large (RPL)

subunits of these proteins and the scarcity of these proteins can cause the development of the disease. These mutations can disrupt the pre-rRNA processing of the 18S rRNA and pre-40S subunits, leading to reduced production of 40S ribosomal subunits. RNA interference can cause a severe defect that alters the normal primary human hematopoietic progenitor differentiation and proliferation of the erythroid progenitor (EP) cells (18)

As per the 'ribosomal stress' mechanism, ribosomal deficiency activates and stabilizes p53, subsequently initiating apoptosis to cause bone marrow failure by terminating cell lines. Murine double minute (MDM2) is a ringer figure ubiquitin ligase that controls the level and activity of p53. When interacting with the normal ribosomal protein, MDM2 enhances p53 degradation. In DBA ribosomal stress, many free RPS builds up due to disrupted ribosomal biosynthesis. The free RPS, such as RPL5, RPL11, RPL23, RPS27, and RPS7, bind with MDM2 to stabilize p53, leading to apoptosis, cell cycle arrest, and eventually erythroid hypoplasia (16).

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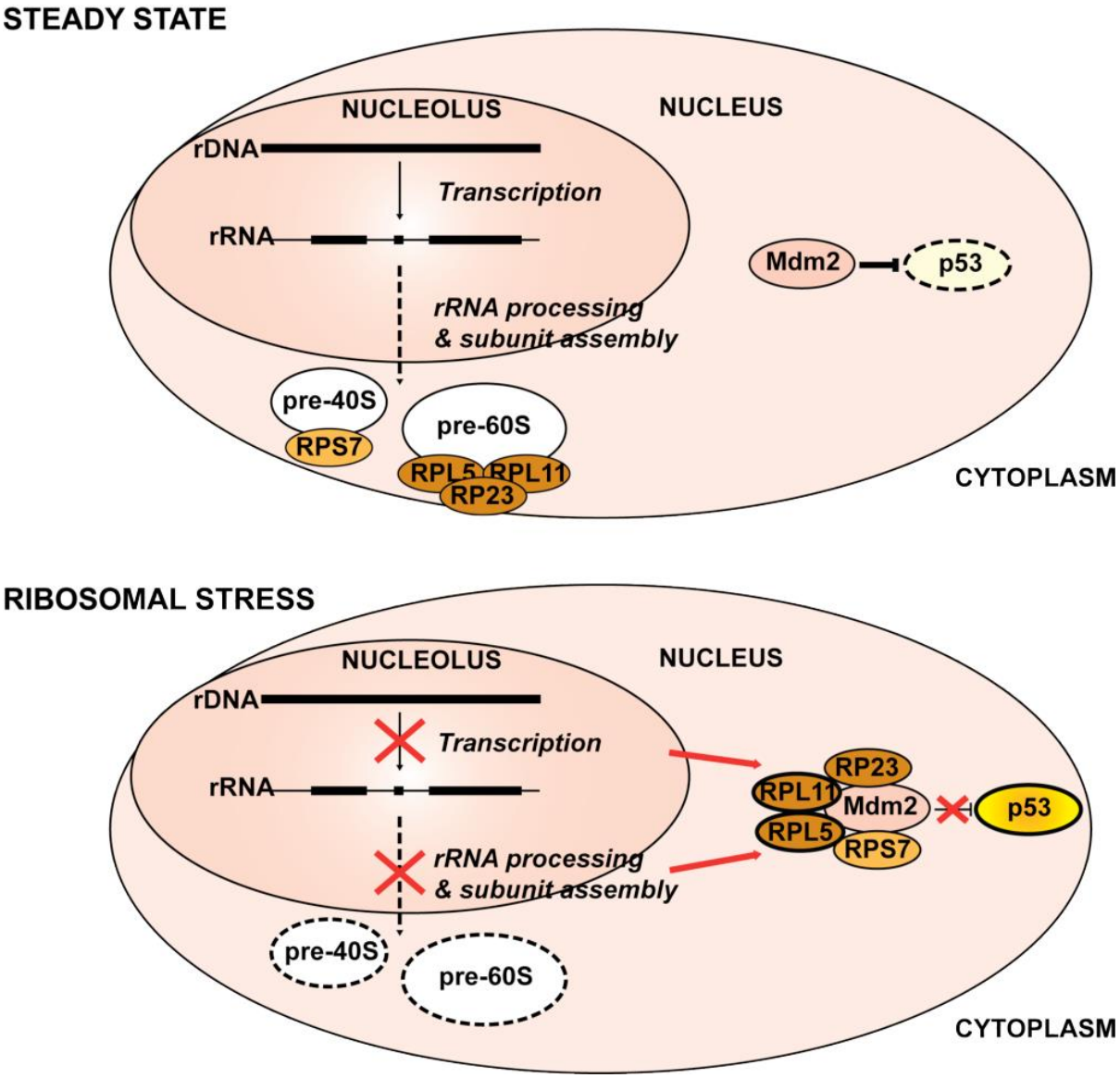

Figure 1: **Pathophysiology of Diamond Blackfan anaemia** (19).

Complications of Diamond Blackfan anaemia

Diamond Blackfan anaemia patients are at high risk of developing a haematological complication in the first year of life (16).

1. Corticosteroids side effects:

The importance of steroid side effects in DBA as illustrated by data from the French registry, which showed complications due to steroid therapy, including hypertension, diabetes mellitus, and

growth retardation, were noted in 20% of patients on long-term steroid therapy. In North America, where steroid dosing and monitoring practices may vary, the DBAR has documented 22% of patients on steroids with pathological fractures and 12% with cataracts. Avascular necrosis, especially affecting the femoral head, is a potential risk and should be investigated in patients with joint pain and stiffness (20). Other side effects of corticosteroids include osteoporosis, weight gain, cushingoid appearance, gastric ulcers, cataracts, glaucoma, and increased susceptibility to infection (21).

Table 2: Summary of corticosteroid side effects (20).

Cosmetic	Hirsuitism, moon face, facial erythema, Weight gain, acne.
Behavioural	Hyperactivity, depression, psychosis
Endocrine	Adrenal suppression, impaired glucose tolerance, diabetes mellitus, menstrual irregularities
Fluid and electrolytes	Hypertension, hypokalaemia, hypocalcaemia
Immunosuppression	Varicella, Pneumocystis pneumonia, candida
Skeletal	Fractures
Gastrointestinal	Gastritis, perforation, pancreatitis

2. Iron overload: Iron is released from the breakdown of red blood cells by macrophages in the reticuloendothelial system. Since iron is not recycled into new red cells in DBA and there is no specific mechanism for excretion, iron accumulates in tissues. Eventually, as the capacity for safe sequestration of the excess iron is surpassed, extensive iron-induced injury develops in the heart, liver, pancreas, thyroid, and other organs. With transfusional iron overload, the onset of toxic manifestations, the pattern of organ involvement and the severity of tissue damage are known to be influenced by a variety of factors, including the magnitude of the body iron burden, the rate of iron loading, the distribution of excess iron between the reticuloendothelial storage compartment and the parenchymal cells of sensitive tissues, and the amounts of non-transferrin-bound iron in the plasma (20).

3. Haematopoietic stem cell transplantation: HSCT also has side effects to take into consideration, including infection and graft versus host disease (GVHD) (16).

Clinical manifestations and laboratory investigations of Diamond Blackfan anaemia
Clinical manifestations of Diamond Blackfan anaemia

Diamond-Blackfan anaemia (DBA) is characterized by early-onset hypoplastic (normocytic, macrocytic) anaemia (21). The median age at presentation and diagnosis of classical DBA are 8 weeks and 12 weeks, respectively (22). Congenital anomalies are observed in approximately 50% of affected individuals and more than one anomaly is observed in up to 25% of individuals.

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Additional features include growth deficiency in about 30 % of affected individuals and predisposition to malignancy. The clinical features include (21):

- Pallor, weakness, failure to thrive.

Anaemia**:** The primary hematologic feature of DBA is a profound normochromic, macrocytic anaemia with normal leukocytes and platelets. The hematologic complications of DBA occur in 90% of affected individuals during the first year of life: the median age at presentation is two months and the median age at diagnosis is three months.

- Congenital malformations (observed in ~30%-50%); in particular craniofacial, upper-limb, heart, and genitourinary malformations

Craniofacial features: include microcephaly; hypertelorism, epicanthus, ptosis; microtia, low-set ears; broad, depressed nasal bridge; cleft lip/palate, high arched palate; micrognathia; low anterior hairline.

Fig 2: Microtia Smaller outer ear than normal. One or both ears can be affected, and ear(s) can look different from normal or be placed lower than normal on the head. The ear canal and internal ear structure can also be malformed.

Eye findings**:** include congenital glaucoma, congenital cataract and strabismus**.**

Neck Features: include webbing, short neck, Klippel-Feil anomaly, Sprengel deformity(21).

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Fig 3: Webbed neck: Abnormal skin folds that run along the side of the neck and down to the shoulders.

Upper limb and hand including thumb**:** Findings include absence of radial artery; flat thenar eminence; triphalangeal, duplex, bifid, hypoplastic, or absent thumb.

Genitourinary findings: include absent kidney, horseshoe kidney; hypospadias.

Heart findings**:** include ventricular septal defect, atrial septal defect, coarctation of the aorta, other cardiac anomalies.

Growth deficiency (observed in 30%)

Growth deficiency**:** Low birth weight was reported in 25% of affected infants. Thirty percent of affected individuals have growth deficiency. Growth deficiency can be influenced by other factors including steroid treatment.

Development**:** Rarely, developmental delay can occur.

Malignancy**:** DBA is associated with an increased risk for acute myelogenous leukemia, myelodysplastic syndrome, and solid tumors including osteogenic sarcoma(21).

Table 3: Frequency of Select Features Diamond-Blackfan Anaemia (21)

Feature	**% of Persons with Feature [1]**	**Comment**
Anaemia	100%	90% in 1st year of life

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Feature	% of Persons with Feature [1]	Comment
Craniofacial features	27%	
Upper limbs anomalies	16%	
Genitourinary malformations	13%	
Heart defects	11%	
Growth deficiency	30%	
Malignancy	2%-5%	Acute myelogenous leukemia, myelodysplastic syndrome, and solid tumors include osteogenic sarcoma, lung, colon, and cervical carcinomas

Laboratory investigations of Diamond Blackfan anaemia

Diamond-Blackfan anaemia (DBA) **should be suspected** in individuals with the following clinical, laboratory, and histopathologic features, and no evidence of another inherited disorder of bone marrow function (21).

Laboratory features

- Macrocytic anaemia with no other significant cytopenias
- Increased erythrocyte mean corpuscular volume
- Reticulocytopenia
- Elevated erythrocyte adenosine deaminase activity (eADA) (observed in 80%-85%)
- Elevated haemoglobin F concentration

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Histopathology features (bone marrow aspirate)

- Normal marrow cellularity
- Erythroid hypoplasia
- Marked reduction in normoblasts
- Persistence of pronormoblasts on occasion
- Normal myeloid precursors and megakaryocytes

The laboratory investigations include:
1. Complete blood count: red blood cell count (reduced), packed cell volume (reduced), haemoglobin concentration (reduced) mean corpuscular volume (>100fL).
2. Reticulocyte count: Reticulocytopenia, a major feature of DBA with absence or 20.109/L reticulocytes, reflecting the bone marrow inability to produce red blood cells.
3. Bone marrow aspirate and bone marrow biopsy: DBA is diagnosed by documenting specific and characteristic erythroblastopenia on bone marrow aspirates or bone marrow biopsies. Absence or, <5% of erythroid precursors on the bone marrow smear (erythroblastopenia) or decreased erythroid cellularity on the bone marrow biopsy in otherwise normal bone marrow cellularity of other cell lines (no sign of dysplasia), no defect in other cell lineage is diagnostic (1).

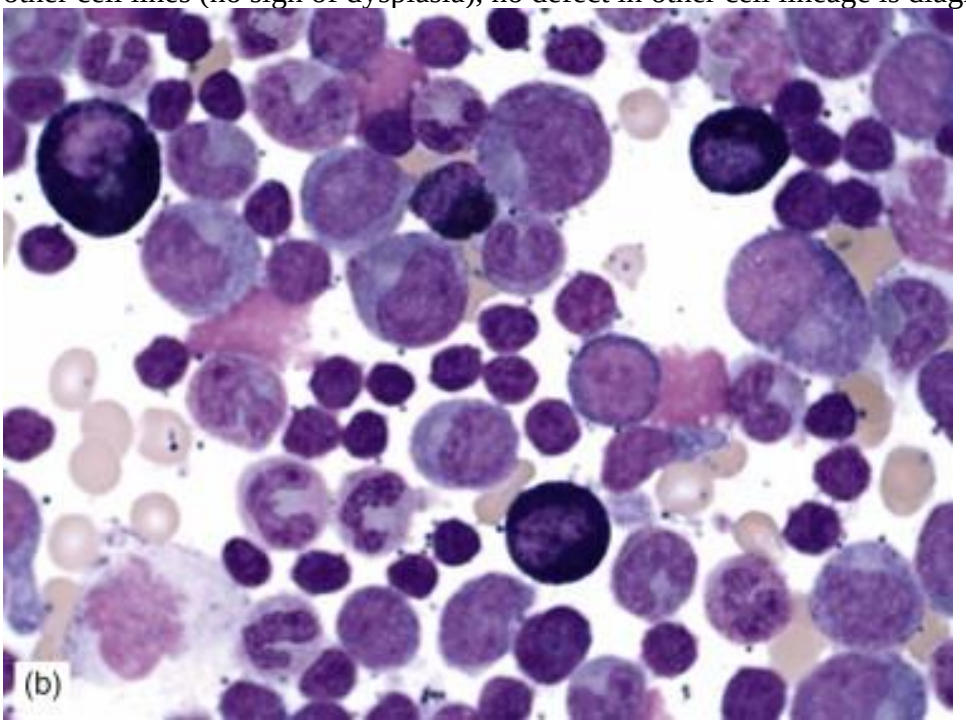

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Fig 4: Bone marrow smear from a patient with pure red cell aplasia demonstrating lack of erythroid precursors x100 (1).

4. Erythropoietin levels: EPO is elevated in DBA. However elevated concentration is nonspecific and it has been suggested that the lack of sufficient numbers of erythroid cells expressing EPO receptors in hypoplastic erythroid bone marrow may contribute to higher EPO levels.

5. Foetal Hb estimation: foetal Hb levels are elevated in DBA and should be measured after the age of 6 months (1).

7. Peripheral blood smear: macrocytic, normocytic red blood cells

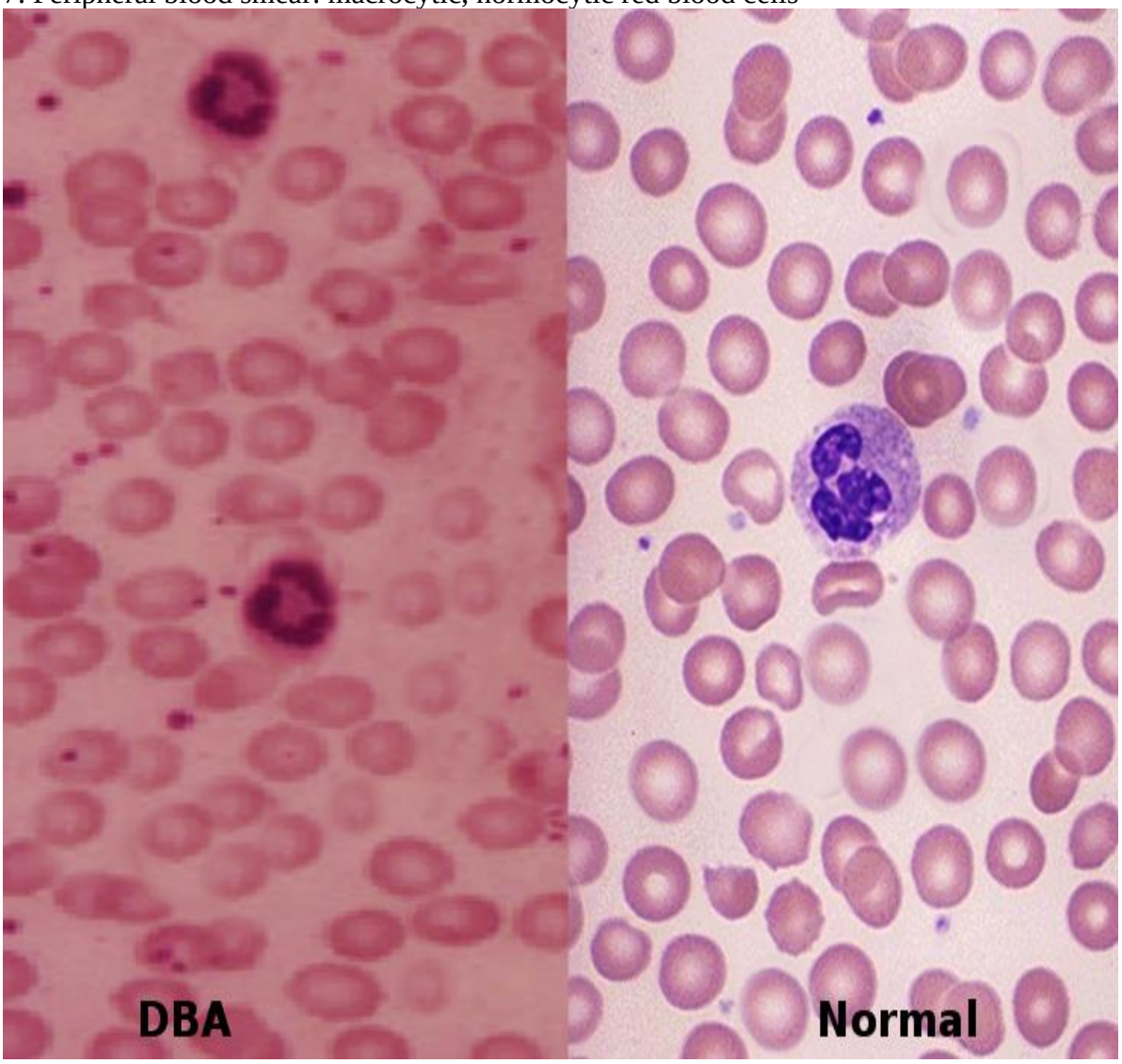

Figure 5: Peripheral blood showing macrocytes x 100 (16).

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6. Radiological examinations:

Differential diagnosis

Transient erythroblastopenia of childhood (TEC) must be ruled out in children as the more common disorder. TEC is an acquired, short-lived failure of red cell production usually of a month or so in duration. As in DBA, children with TEC often present with profound anaemia. TEC is most likely a post-infectious, transient autoimmune IgG-mediated disorder characteristically occurring in toddlers probably as a result of infections acquired through contact with playmates. Most important, a positive family history and congenital anomalies are not characteristic of TEC. Elevated foetal haemoglobin levels and macrocytosis, common presenting features in DBA, are only seen in TEC upon recovery as a consequence of so-called "stress erythropoiesis". Of note macrocytosis is often obscured in the newborn period by residual foetal erythrocytes and also can be masked by concomitant thalassemia minor or iron deficiency and other cytopenias are found in both disorders. Although the mechanism is unknown, an elevated erythrocyte adenosine deaminase activity is found in about 85% of patients with DBA and none with TEC. Thus the two disorders can usually be distinguished. The use of limited packed red cell transfusions to achieve a haemoglobin level that will not inhibit erythroid recovery is recommended, particularly when the diagnosis is unclear. Once the diagnosis is made definitive treatment for DBA can commence (22).

Table 4: Differential diagnosis of DBA versus TEC (22).

	Diamond Blackfan Anaemia (DBA)	**Transient Erythroblastopenia of Childhood (TEC)**
Pure red cell aplasia	Present	Present
Age	Younger than 1 year	Older than 1 year
Inheritance	Sporadic and dominant inheritance. Mutation analysis as available.	Not inherited
Congenital abnormalities	Present	Absent
Mean corpuscular volume (MCV)	Elevated	Normal (may be elevated upon recovery)
Foetal Haemoglobin	Elevated	Normal (may be elevated upon recovery)
Erythrocyte ADA (eADA) activity	May be present	Normal

Treatment

Non pharmacological interventions

Corticosteroids therapy: Corticosteroids remain the mainstay of treatment in DBA for more than half a century after the original report of their efficacy in 1951. Their mechanism of action in DBA is still unknown and under investigation. Approximately 80% of DBA patients respond to an initial

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course of steroids (20), 17% were non-responsive and 4% of patients were never treated with steroids (22). The recommended corticosteroid is prednisone with a starting dose of 2 mg/kg/day given orally once a day in the morning, beginning after age 12 months and ten days to two weeks after a transfusion. An increase in haemoglobin and reticulocyte count is usually seen in two to four weeks. If there is no response by three weeks, steroids can be tapered over two weeks. Corticosteroids may be slowly tapered to the minimal effective dose. Monitoring of blood counts is essential to ensure that the red cell haemoglobin concentration remains at 80-100 g/L, the minimum required for transfusion independence. The corticosteroid maintenance dose varies and can be extremely low in some individuals. Concerns about the long-term effects of steroids have led to the recommendation of 0.25 mg/kg/day as a preferable maximum daily dose (21). In over 20% of DBA patients, steroids (or red cell transfusions) may eventually be stopped completely with continued maintenance of adequate haemoglobin levels, a so-called "remission" or more appropriately, treatment independence (20).

There is no general consensus on steroid therapy, some consensus participants recommend a steroid trial beginning at one year of age**,** generally it is not recommended in babies under 6 months of age due to lack of evidence that a delay in starting a trial of steroids affects responsiveness. However, an earlier trial of steroids may be considered if there is poor venous access, or where the safety of the blood supply is questionable. When steroids are started in babies less than 1 year of age, growth and neuromotor development should be closely monitored. A repeat trial of steroids may be considered for nonresponders, as response to a second course has been described anecdotally (20).

Pharmacological interventions

Transfusion therapy: At birth and during infancy, haemoglobin (Hb) level may be either normal or below normal, but the need for transfusion begins before the age of 1 year in 90% of patients (1), to reduce corticosteroid associated side effects and adverse effects in neonates which may include noteworthy growth disturbances (18). The international consensus is not to use glucocorticoids before the age of 1 year, and this may be further delayed in children with severe growth failure. The threshold for transfusion is 80 to 90 g/L (1). Chronic transfusion therapy with packed red blood cells is begun once it has been established that the patient is not responsive to corticosteroids (18). The goal of transfusion therapy is a red cell haemoglobin concentration of 80-100 g/L, which is usually adequate for maintaining growth and development (21).

Hematopoietic stem cell transplantation (HSCT): is the only curative therapy for DBA. Individuals with DBA who are transfusion dependent or develop other cytopenias are often treated with HSCT. Allogeneic SCT is more preferable than alternative donor SCT due to its high survival rate and reduced risk of complications (22). HSCT has a high success rate in patients less than 10 years of age treated with an HLA-identical donor (16). Bone marrow is the most common source of stem cells; however, four unrelated cord blood and one unrelated peripheral stem cell transplants have been performed. In general, patients with DBA, whether steroid-responsive or transfusion-dependent, may be considered for transplant prior to age 10 years, and preferably between the ages

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of 2 and 5 years, if an HLA-matched related donor is available. This is particularly true for transfusion-dependent patients, in whom iron overload, is a significant adverse prognostic factor (20).

Treatment of other manifestations

- Glaucoma and cataract**:** As recommended by ophthalmologist
- Skeletal anomalies**:** Surgical management of thumb anomalies as recommended by orthopedist; occupational and physical therapy as needed
- Genitourinary malformations**:** Managed as recommended by nephrologist and/or urologist
- Congenital heart defects**:** As recommended by cardiologist
- Cancer: Treatment of malignancies coordinated by oncologist

Prevention of secondary complications and management
Prevention of complications of Diamond Blackfan anaemia

Transfusion iron overload: is the most common complication in transfusion-dependent individuals. The following methods are used both to assess for evidence of transfusion iron overload and to evaluate the effectiveness of iron chelation therapy:

- Measurement of iron concentration in a liver biopsy specimen, which accurately determines total body iron accumulation
- Magnetic biosusceptometry (SQUID), which gives a measurement of hepatic iron concentration

Note:

(1) Although the latter methods of total iron measurement is non-invasive, SQUID is not widely available. MRI is now more widely available and referral to a center with experience in this technique is advisable to obtain a baseline measurement and to more conveniently follow progress after starting chelation therapy. Although liver biopsy is the "gold standard" it is not a practical choice for long-term follow up.

(2) Routine measurement of serum ferritin concentration is not reliable in detecting iron overload because the serum ferritin concentration does not always correlate with total body iron accumulation (21).

Iron chelation therapy: is usually started after ten to 12 transfusions (170-200 mL/kg of packed red blood cells), when serum ferritin concentration reaches 1,000-1,500 µg/L, or when hepatic iron concentration reaches 6-7 mg/g of dry weight liver tissue.

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- Deferasirox: is recommended in individual's age two years or older. It is administered once daily in an oral dose of 20-30 mg/kg/day. Side effects are usually mild and include rash, nausea, creatinine elevation, and rarely proteinuria and transaminase elevation. In affected individuals, satisfaction with deferasirox is greater than with desferrioxamine, mostly because of ease of administration.
- Desferrioxamine: is administered four to seven nights a week in an eight- to 12-hour subcutaneous infusion via a portable pump. The recommended initial dose is 40 mg/kg/day; the maximum dose is 50-60 mg/kg/day. The dose and frequency of infusion may be modified using the serum ferritin concentration or the hepatic iron concentration as a guide. Side effects include ocular and auditory toxicity and growth deficiency.

Note:

(1) In affected individuals, satisfaction with deferasirox is greater than with desferrioxamine, mostly because of ease of administration.

(2) Deferiprone is not recommended in the treatment of iron overload in individuals with DBA because its side effects include neutropenia (21).

Management of Diamond Blackfan anaemia

Patients with DBA should be monitored with complete blood counts frequently. Periodic bone marrow biopsy or aspiration to evaluate cellularity and morphology helps diagnose any new cytopenias or bone marrow failure. Patients who are steroid-dependent or transfusion-dependent should be monitored for blood pressure and growth as they are at high risk of organ failure; often, an endocrinology consult is necessary. Healthy DBA patients need to follow up every 4 to 6 months with history, physical examination, and complete blood count for cancer surveillance. The rapid decline of any cell line indicates bone marrow failure, and bone marrow biopsy with cytogenetic studies is required to diagnose chromosomal abnormalities associated with cancer (20).

Conclusion

DBA is a rare genetic blood disorder that affects the production of red blood cells and can cause a range of symptoms. Early diagnosis and treatment are important for managing the condition and preventing complications. Ongoing research is needed to better understand the molecular pathogenesis of DBA and to develop more effective treatments for this rare disorder.

Conflict of Interest: The authors have declared no conflict of interest.

References

1. Da Costa, L., Leblanc, T., Mohandas, N. (2020). Diamond-Blackfan anaemia. *Blood, The Journal of the American Society of Haematology*; **136(11)**:1262-1273.
2. Flygare, J., Karlsson, S. (2007). Diamond-Blackfan anaemia: erythropoiesis lost in translation. *Blood*; **109(8)**:3152–3154. 11.Diamond, L.K., Allen, D.W., Magill, F.B.

Citation: Onuigwe FU, Asmau UA, Uchechukwu NJ Obeagu EI. Reviewing Erythrocyte Morphology Changes in Hemophilia Patients with HIV: Current Insights. *Elite Journal of Haematology, 2024; 2(5):* 108-125

(1961). Congenital (erythroid) hypoplastic anaemia a 25 year study". *American Journal Disease of Children*;**102 (3)**: 403–415

3. Bartels, M., Bierings, M. (2019). How I manage children with Diamond-Blackfan anaemia. *British journal of haematology*; **184(2)**: 123–133.
4. Ball S. (2011). Diamond Blackfan anaemia. *American Society of Haematology Education Program*; **2011(1)**: 487–491.
5. Young, N.S., Alter, B., (1994). Inherited bone marrow failure syndromes: introduction. *Aplastic anemia acquired and inherited*; **1**:271-274.
6. Da Costa, L., Narla, A., and Mohandas, N. (2018). An update on the pathogenesis and diagnosis of Diamond-Blackfan anemia. *F1000Research*, *7*, F1000 Faculty Rev-1350.
7. Gripp, K.W., McDonald-McGinn, D.M., La Rossa, D., McGain, D., Federman, N., Vlachos, A., Glader, B.E., McKenzie, S.E., Lipton, J.M., Zackai, E.H. (2001). Bilateral microtia and cleft palate in cousins with Diamond-Blackfan anaemia. *American journal of medical genetics*; **101(3)**:268-274.
8. Lipton, J.M., Federman, N., Khabbaze, Y., Schwartz, C.L., Hilliard, L.M., Clark, J.I., Vlachos, A. (2001). Osteogenic Sarcoma Associated With Diamond Blackfan Anaemia: A Report From the Diamond Blackfan Anaemia Registry. *Journal of paediatric haematology/oncology*; **23(1)**:39-44.
9. Dianzani, I., Garelli, E. and Ramenghi, U. (1996). Diamond-Blackfan anaemia: a congenital defect in erythropoiesis. *Haematologica*; **81(6)**:560-572.
10. Diamond, L.K., Allen, D.W., Magill, F.B. (1961). Congenital (erythroid) hypoplastic anaemia a 25 year study". *American Journal Disease of Children*;**102 (3)**: 403–415.
11. Ulirsch, J. C., Verboon, J. M., Kazerounian, S., Guo, M. H., Yuan, D., Ludwig, L. S., Handsaker, R. E., Abdulhay, N. J., Fiorini, C., Genovese, G., Lim, E. T., Cheng, A., Cummings, B. B., Chao, K. R., Beggs, A. H., Genetti, C. A., Sieff, C. A., Newburger, P. E., Niewiadomska, E., Matysiak, M., Gazda, H. T. (2018). The Genetic Landscape of Diamond-Blackfan Anaemia. *American journal of human genetics*; **103(6)**:930–947.
12. Iskander, D., Roy, N. B. A., Payne, E., Drasar, E., Hennessy, K., Harrington, Y., Christodoulidou, C., Karadimitris, A., Batkin, L., de la Fuente, J. (2023). Diamond-Blackfan anaemia in adults: In pursuit of a common approach for a rare disease. *Blood reviews*; **61(1)**:101-197.
13. Ulasi T.O., Nri-Ezedi C.A., Ofiaeli O.C., Chijioke E.G. (2021). Novel Cases of Diamond Blackfan Anaemia in Two Nigerian Toddlers: Roadmap for Care in Resource-Limited Nations. *International Journal of Scientific Research in Dental and Medical Sciences***; 3(2):**101-104.
14. Da Costa, L. M., Marie, I., Leblanc, T. M. (2021). Diamond-Blackfan anaemia. *Haematology. American Society of Haematology Education Program***; 2021(1)**: 353–360.
15. Mirabello, L., Khincha, P.P., Ellis, S.R., Giri, N., Brodie, S., Chandrasekharappa, S.C., Donovan, F.X., Zhou, W., Hicks, B.D., Boland, J.F., Yeager, M., (2017). Novel and

Citation: Onuigwe FU, Asmau UA, Uchechukwu NJ Obeagu EI. Reviewing Erythrocyte Morphology Changes in Hemophilia Patients with HIV: Current Insights. *Elite Journal of Haematology, 2024; 2(5):* 108-125

known ribosomal causes of Diamond-Blackfan anaemia identified through comprehensive genomic characterisation. *Journal of medical genetics*; **54(6)**:417-425.
16. Gadhiya K, Wills C. (2023). Diamond Blackfan Anaemia. [Updated 2023 Mar 14]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023
17. Liu, Y. L., Shibuya, A., Glader, B., Wilkes, M. C., Barna, M.,Sakamoto, K. M. (2023). Animal models of Diamond-Blackfan anemia: updates and challenges. Haematologica; **108(5)**:1222–1231.
18. Engidaye, G., Melku, M., Enawgaw, B. (2019). Diamond Blackfan Anaemia: Genetics, Pathogenesis, Diagnosis and Treatment. *Electronic journal of the international federation of clinical chemistry and laboratory medicine*; **30(1):** 67–81.
19. Jaako, P. (2012). Modelling Diamond-Blackfan Anaemia in the Mouse: Disease Pathogenesis and Evaluation of Novel Therapies.
20. Vlachos, A., Ball, S., Dahl, N., Alter, B. P., Sheth, S., Ramenghi, U., Meerpohl, J., Karlsson, S., Liu, J. M., Leblanc, T., Paley, C., Kang, E. M., Leder, E. J., Atsidaftos, E., Shimamura, A., Bessler, M., Glader, B., Lipton, J. M. (2008). Diagnosing and treating Diamond Blackfan anaemia: results of an international clinical consensus conference. *British journal of haematology*; **142(6):** 859–876.
21. Sieff, C. (2009) Diamond-Blackfan Anaemia. In: Statpearls
22. Lipton, J. M., Ellis, S. R. (2010). Diamond-Blackfan anaemia: diagnosis, treatment, and molecular pathogenesis. *Haematology/oncology clinics of North America*; **23(2)**: 261–282.
23. Sieff C. Diamond-Blackfan Anemia. 2009 Jun 25 [Updated 2023 Mar 23]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK7047/
24. Ball, S.E., McGuckin, C.P., Jenkins, G., Gordon-Smith, E.C. (1996). DiamondBlackfan anaemia in the UK: analysis of 80 cases from a 20-year birth cohort. *B Journal Haematology*; **94**:645-653.
25. Kaushansky, K., Lichtman, M., Beutler, E., Kipps, T., Prchal, J., Seligsohn, U. (2010). "35". *Williams Hematology* (8th ed.). McGraw-Hill. 2350
26. Vlachos, A., Muir, E. (2010). How I treat diamond-Blackfan anaemia. *Blood, The Journal of the American Society of Haematology*; **116(19)**:3715-3723.

Citation: Onuigwe FU, Asmau UA, Uchechukwu NJ Obeagu EI. Reviewing Erythrocyte Morphology Changes in Hemophilia Patients with HIV: Current Insights. *Elite Journal of Haematology, 2024; 2(5):* 108-125