Case study

BEYOND ANEMIA : A COMPREHENSIVE CASE STUDY ON DIAMOND BLACKFAN ANEMIA

ABSTRACT

Diamond blackfan syndrome is a rarest anemic disease with characteristics of small jaw & wide set eyes, etc. It is gentical disorder rating a low incidence rate world wide. The diagnostic criteria is mainly based upon the clinical presentation, laboratory investigation and genetic testing. The primary treatment includes corticosteroids, iron chelation therapy, blood transfusion and so on.

Case presentation: A child admitted with a complaints excessive cry, pallor, multiple episodes of convulsion, At presentation child was hemodynamically stable, pallor was positive. On clinical laboratory investigations, child is genetically proven diamond blackfan anemia. The primary treatment was initiated.

Conclusion: DBA being a rare gentical disorder , corticosteroids remain the first-line treatment, while transfusions are employed to alleviate anemia-related symptoms. Bone marrow transplantation offers the potential to enhance patient outcomes.

INTRODUCTION

Diamond black fan syndrome is a rare congenital hypoplastic anemic disease that is characterized by red cell aplasia, short stature and physical abnormalities such as small jaw, wide-set eyes, a flat nasal bridge, or a small or deformed head (microcephaly) and structural anomalies . usually becomes symptomatic in early infancy, often with the pallor in the neonatal period. The main characteristic hematological features are macrocytic anemia reticulocytopenia and red blood cell precursors associated with the failure of erythropoiesis and normal production of platelets and leucocytes in a cellular bone marrow.[1]

CLINICAL MANIFESTATIONS

- Pallor
- Microcephaly
- Retardation of growth
- Developmental delay
- Congenital anomalies such as cleft palate, kidney or heart issues • Blood cell lineage defect [2]

EPIDEMIOLOGY

DBA is a heterogeneous gentical disorder with an incidence rate of 7 cases per million births are affected annually. That means 23-35 new infants are born in the US each year. For every million births , there are 7 cases of Diamond blackfan Anemia ,an uncommon congenital disease and also been diagnosed at birth in 13% - 16%.Both the genders are equally affected[3]

ETIOLOGY

- DBA is a disease associated with the major defect of disordered erythropoiesis, the genes responsible for this is disease belongs to both small and large subunits of ribosome.
- Mutated Genes such as RPS19, RPL5, RPL11 and RLP35A are responsible for the protein synthesis in most of the DBA cases.
- GATA1 gene mutations which are responsible for decreased erythropoiesis in the DBA cases .

Inherited patterns:

- Autosomal dominant Inheritance [single copy of inherent defective gene from one parent]
- Denovo mutations[spontaneously occurring of mutation in the patient nor its been inherited from the parents]
- Unknown causes
- Environmental factors may trigger the the condition of genetically predisposed individuals
- X linked inheritance [It's a rare and males are more severely affected due to presence of only one X chromosome][4]

RISK FACTORS

- Immunocompromised patients
- Genetic mutations
- Family history
- Environmental factors
- Developmental delay

DIAGNOSIS

The diagnostic criteria is mainly based upon the clinical presentation, laboratory investigation and genetic testing.

Clinical presentation: Most DBA patients are diagnosed by 3 months of age.

DBA associate with congenital physical anomalies, such as

- Thumb and upperlimb malformations such as triphalangeal , bifida accessory, absent , hypoplastic, subluxed thumbs, unilaterally or bilaterally.

- Eye anomalies such as glaucoma, hypertelorism, cataract, microphthalmos , anophthalmos.
- Craniofacial anomalies such as short stature
- A cute snub nose and wide spaced eyes
- Urogenital anomalies, atrial or ventricular spetal and prenatal or postnatal growth retardation.

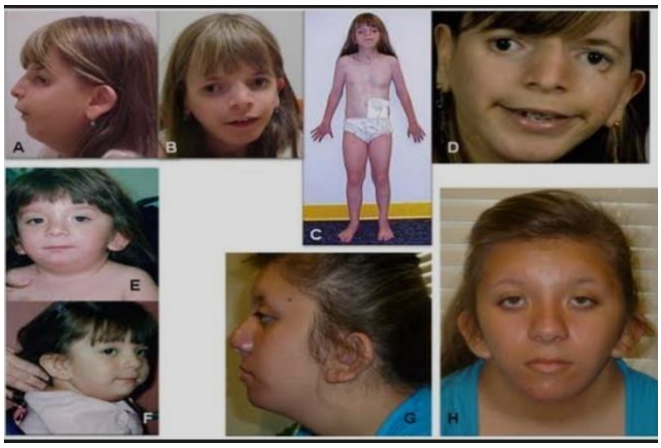

Figure 1 : Represents the signs of children with diamond black fan anemia.[5]

Differential diagnosis

- Laboratory investigation:
- Macrocytic moderate to severe anemia
- Reticulocytopenia
- Paucity of erythroid precursor cells in the bone marrow testing [verifies the aplasia of red blood cells].

Genetic testing

- Genetic screening for sequencing of RPS19[Ribosomal protein mutants is responsible for a defect of rRNA maturation, which is significant feature for most DBA cases]
- RPL5 [Gene mutation responsible for cleft palate malformation in DBA cases]
- RPL15 [Gene mutations have been identified in cases of hydrous fetalis in DBA patients]
- RPL11[Gene mutations are associated with classic triphalangeal thumb]
- RLP35a [Gene mutations associated with neutropenia].[6]

TREATMENT

1. Corticosteroids

It is the main treatment for Diamond blackfan syndrome , usually drugs such as prednisolone or prednisone are used in the treatment. Most of the patient show an increasable increase in the hemoglobin levels within 2-4 weeks after the initial start of steroidal course .

Dosage : Initial high dose is preferred, the dose is tapered to determine the minimum dosage required for continuing transfusion independence. The preferred dose is 2mg/kg of prednisone, or glucocorticoid equivalent, given as single daily dose in the morning. If transfusion independence is not achieved, the steroids should be tapered and discontinued.

2. Blood transfusion

Chronic transfusion therapy with packed red blood cells begun if the patient is not responsive to the corticosteroids. The main goal of transfusion therapy is to increase the hemoglobin levels high for maintaining adequate growth and development. Regular blood transfusions to keep hemoglobin levels stable (every 3-5 weeks).

3. Iron chelation therapy:

In patients receiving monthly transfusions, the hepatic iron concentration would predicted to be rise from ideal range(3-7mg/g, dry weight) to high risk range(>15mg/g, dry weight)in just 12 months .So to maintain Iron overload after recurrent transfusion iron chelation therapy is used. Gold standard for measuring hepatic iron concentration is through liver tissue biopsy, magnetic suspectometry(SQUID) and magnetic resonance imaging (MRI). When hepatic iron concentration has reached 6-7mg/g dry weight Chelation therapy should be initiated. Medications such as Deferoxamine at dose of 40mg/kg sc over 8-12h for 4-6 nights/week should be initiated, Deferiprone of doses 20-30 mg/kg/day stabilize or decrease the iron overload.

4. Hematopoietic stem cell transplantation

In DBA patients, whether steroid irresponsive or transfusion independent, may be considered for HSCT, if an HLA matched related donor or umbilical cord blood transfusion is available.

5. Other treatments

These drugs are ineffective and currently have no evidence, but specific patients may respond hence they are used over several years in the treatment of DBA

Cyclosporine, Metoclopromide,Androgens, high dose corticosteroids, Erythropoietin, interleukin-3, Valproic acid, leucin etc [(7)]

COMPLICATIONS

- Cancer including hematological malignancy and solid tumors
- Iron overload
- Endocrine dysfunction including growth impairment, hypocortisolism, osteoporosis, avascular necrosis, diabetes and puberty delay
- Lifelong anemia
- Myeloid leukaemia plastic syndrome, acute myeloid leukaemia, colon carcinoma and osteogenic sarcoma.[(8)]

CASE PRESENTATIONS:

Here is 7 months old female child 1st born to NCM(non consanguineously marry) couple with normal antenatal history born through LSCS I/V/O RDS baby was admitted for 3 days. Child was admitted multiple times for blood transfusion.

On 1st admission , 1.5 month of age presented as excessive cry, pallor, multiple episodes of convulsion, I/V/O refractory convulsions child was put on inj ,Levipill and valproate and mechanically ventilated for 3 days , HB-2gm, PCV-6, MCV-122, APPT/PT/INR32/40/2.2,FFP was transfused. Child was suspected to have IC bleed I/V/O multiple convulsions and low HB. Inj tranexamic acid and vitamin k given for 3 days, diagnosis was made as late onset sepsis however USG sonogram there is no intra parenchymal bleed, discharge on syrup Levipill 0.4 ml(20mg/kg/day).

On 2nd admission, 2m-Low HB-1 PRBC transfusion, repeat hb-12.9, 3 rd admission @ 4m 12 D-low hb-4.3 gm-PRBC transfusion given. 4th admission @ 7 M- yellowish discoloration, hb -2.8gm,2 PRBC given, repeat hb-7.7gm, last transfusion. Hb electrophoresis-normal HbF-1.60, HbA-957, HbA-2.7. Retic count-0.1, PS+ dimorphic picture, suspected to be bone marrow failure syndrome, pure cell aplastia reffered here to IGICH. At presentation child was haemodynamically stable, pallor +, no icterus, no other complaints.

Issues addressed:

Anemia- child is genetically proven diamond blackfan anemia, child was pale looking and signs of failure was noted.

Bone marrow report : normocellular marrow exhibiting marked erythroid suppression.

Lactate levels-35.4 ruled out pearson syndrome.

OBJECTIVE EVIDENCES:

CNS : Conscious, alert, bilateral pupil are equally reactive.

CVS : S1 S2+, No murmur.

RS : B/L air entry+, B/L NVBS +,no added sounds.

PA : Soft, non tender.

HR: 136 bpm.

RR : 30 cpm.

SPO2 : 98%.

CRT : <3 sec.

BP:91/79 mm/hg.

Temperature: Afebrile.

Weight : 5.2 kg(3rd centrile)

Height : 62cm(3rd to 50th centrile)

chart 1. LABORATORY INVESTIGATIONS:

LABORATORY INVESTIGATIONS:

SL NO	TEST	1st M	2nd M	4th M	7th M B/A	9th M B/A	10th M B/A	1 Y B/A	1 Y, 1ST MONTH A	1 Y, 2ND MONTH A
1	Haemoglobin	2	12.9	4.3	7.8/10.6	6.3/8.8	5.5/14.7	6.3/10.7	6.7	8.2
2	White blood cells				11200/9000		14700	26700/20,100	13800	10900
3	Neutrophils				45/38		39	32/39	27	35
4	Lymphocytes				44/50		53	59/50	61	53
5	platelets				3.5/4.29		5.9 L	5.28/4.6 L	5.4 L	4.8 L

chart 2. TREATMENT CHART:
TREATMENT CHART:

SL NO	MEDICATIONS	DOSE	ROUTE	FREQUENCY
1	Syrup Levetiracetam	0.5 ml (15mg/kg/d)	PO	BD
2	Syrup Calcium	5 ml	PO	OD
3	Syrup Vitamin D3	2.5ml	PO	OD
4	Syrup A to Z (Multivitamin)	2.5 ml	PO	BD
5	Syrup Vitamin B complex	2.5 ml	PO	BD
6	Syrup Iron+Folic acid+ Vitamin B12(Tonoferon)	1.5 ml	PO	OD
7	Injection Augmentin	For 5 days	IV	

chart 3. DISCHARGE MEDICATIONS:

DISCHARGE MEDICATIONS:

SL NO	MEDICATIONS	DOSE	ROUTE	FREQUENCY
1	Syp Iron + Folic acid+ Vitamin B12 (Tonoferon)	1.5 ml	PO	OD
2	Syrup Calcium	5ml	PO	BD
3	Syrup vitamin D3	1 ml	PO	OD
4	Syrup folic acid	5mg	PO	Weekly once
5	Syrup Levetiracetam	0.5ml	PO	BD

Patient counselling

- Frequent monitoring of hemoglobin levels by blood tests to track organ function.
- Addressing the growth impairments, birth defects and other disease related issues.
- Ensuring sufficient nourishment to promote growth and development.
- Screening for genetic mutations associated with DBA in family members
- A balanced diet rich in iron can support overall health
- Regular followup with an hematologist to monitor the disease and adjust treatments , periodic examinations for any complications like cancer or organ failure.

DISCUSSION

The etiology is mainly due to mutations in genes that encodes Ribosomal proteins , which makes difficulty for assembly and functions of Ribosomal proteins. These may lead to blockage in the development of erythrocyte precursors , finally leading to anemia.

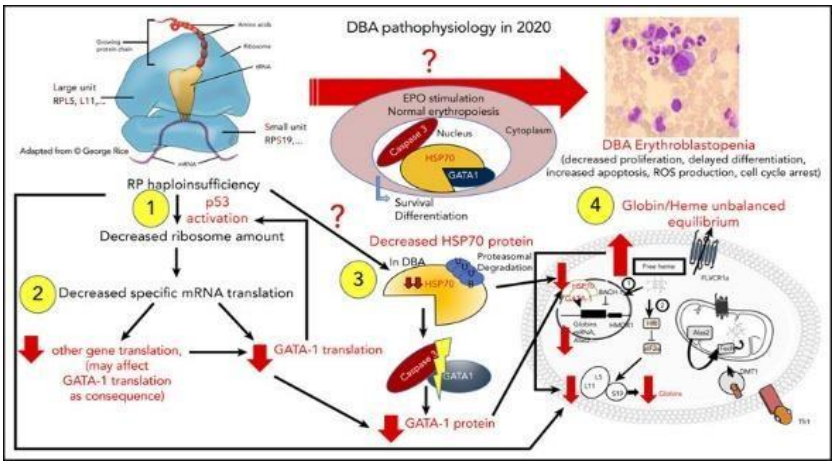

Figure 2 : Represents the pathophysiology of Diamond blackfan Anemia.[9]

Mutations in the Ribosomal proteins such as, RPS19 , Ribosome biogenesis. Leading to haploinsufficiency (Mutations in these Ribosomal gene , with loss of function in a single copy of the gene. Reduced translation initiation, Increased apoptosis due to negative impact on hematopoietic progenitor cell differentiation and production

P53 activation

As per Ribosomal stress mechanism, Ribosomal deficiency stabilizes and activate P53. Initiating aptosis leading to bone marrow failure by terminating cell lines

MDM2[Murine double minute] when interacts with Ribosomal proteins, it enhances P53 degradation. In DBA , these interaction may lead to apoptosis, cell cycle arrest and erythroid hypoplasia due to disrupted Ribosomal biosynthesis

Non RP gene mutations

Non RP gene mutations includes GATA1 mutations, GATA1 mutations on the X chromosome results in the substitution of leucine for valine, effecting the splicing process of GATA1 , and termination of GATA1. Leading to Global translation blockade.[10,11]

Where as in this case, a 7 months child was admitted to the hospital with the complaint of repeated blood transfusion, and symptoms of pallor. On the systemic and laboratory investigation , the bone marrow biopsy resulted in Diamond blackfan syndrome. Syrup Levipill was given to treat refractory seizure, Syrup Calcimax was given to treat calcium deficiency Syrup Vitamin D3 was given to treat low immunity, Syp A to Z was given to treat vitamin deficiency , syrup Meconerv was given to treat vitamin deficiency, syrup Tonoferon was given to treat nutritional deficiencies, Injection Augumentin was given to treat bacterial infection

CONCLUSION

Diamond–Blackfan Anemia (DBA) is a rare and genetically heterogeneous disorder characterized by bone marrow failure resulting in hypoplastic anemia and associated congenital anomalies. Advances in molecular diagnostic techniques have contributed to a deeper understanding of the underlying pathogenic mechanisms, facilitating more accurate diagnosis and enabling the development of targeted therapeutic interventions. Current

management strategies primarily include corticosteroid therapy, chronic red blood cell transfusions, and hematopoietic stem cell transplantation. Among these, corticosteroids remain the first-line treatment, while transfusions are employed to alleviate anemia-related symptoms. Bone marrow transplantation offers the potential to enhance patient outcomes and reduce longterm complications. Continued research efforts are essential to refine treatment protocols and improve the quality of life for affected individuals.

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