TRANSFUSION DEPENDANT ANEMIA IN AN INFANT: A DIAGNOSTIC CHALLENGE
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CASE DETAILS

CHIEF COMPLAINTS:
- 8 month old boy baby
- H/o anemia requiring frequent transfusions since birth.
- Failure to thrive

- DOB: 22.07.14
- Preterm- 33wks (emergency LSCS- absent flow in umbilical artery, IUGR)
- LBW- 1.63kg
- Pallor, icterus, splenomegaly+
**COURSE IN THE HOSPITAL**

- No ABO/Rh incompatibility
- DCT negative
- Peripheral smear
- Nucleated RBCs
- Reti count: 6.2%
- MCV: 146 fl

**ANEMIA + HYPERBILIRUBINEMIA**

- Peak SBR: 20.72 mg/dl
- Hb: 10.7 mg/dl

Intense phototherapy
Exchange transfusion

**Day 0 (22.07.14)**

**Day 3**

Hb: 10.9 mg/dl

TSH: 81.401 mIU/l

1 PRBC

**Day 5**

Hb: 10.9 mg/dl

T. Thyronorm: 12.5 mcg

1 PRBC

**Day 7**

15 days of NICU admission

**CONGENITAL HYPOTHYROIDISM**

**ANAEMIA**
PERIPHERAL SMEAR

Dimorphic anemia

MICROCYTES

MACROCYTES
• **DD’s in the neonatal period:**
  1. Hemolytic disease of newborn
  2. Hereditary spherocytosis
  3. Congenital viral infections
- FISH, Karyotyping reports - normal study
- ECHO - small ASD
- USG abdomen - normal study

- Mother - H/o varicella in 1st trimester of pregnancy
  TORCH (-HIV, VDRL, TOXOPLASMA RUBELLA, CYTOMEGALO VIRUS, HERPES) IgM, IgG - Negative

- Opthalmological examination - normal study
- USG CRANIUM - Normal study
<table>
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<tr>
<th>Months</th>
<th>WEIGHT</th>
<th>ANEMIA</th>
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<tbody>
<tr>
<td>1</td>
<td>1.74kg</td>
<td>PRBC</td>
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<tr>
<td>1.5</td>
<td>1.76kg</td>
<td>Hb 5.6</td>
</tr>
<tr>
<td>2</td>
<td>1.84kg</td>
<td>PRBC</td>
</tr>
<tr>
<td>3</td>
<td>1.92kg</td>
<td>PRBC</td>
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</table>

**ANEMIA**
- PRBC

**Hb in g/dl**
- 4.7
- 5.6
- 6.2
- 7.2
CLINICAL EXAMINATION

Chronological age: 8mths
Corrected age: 6mths 1wk

- WEIGHT - 2.775kg
- LENGTH - 51cm
- HC - 37.5cm
- AF - 4*4 cm
- NO DYSMORPHISM
- PALLOR +
- No icterus
- Eyes - normal
- Abdomen - Moderate spleenomegaly +
## SERIAL CBC

<table>
<thead>
<tr>
<th>DATE</th>
<th>HB (g/dl)</th>
<th>MCV (fl)</th>
<th>Corrected retic (%)</th>
<th>TC</th>
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<tbody>
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<td>22 july 14</td>
<td>10.7</td>
<td>146</td>
<td>6.2</td>
<td>Corrected for nucleated rbc - 2500</td>
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<td>82.8</td>
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<td>DATE</td>
<td>HB</td>
<td>MCV</td>
<td>CORRECTED RETIC (%)</td>
<td>TC</td>
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<td>5 JAN 15</td>
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<tr>
<td>13 FEB 15</td>
<td>8.2</td>
<td>115.9</td>
<td></td>
<td>15300</td>
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DIFFERENTIAL DIAGNOSIS

• Hereditary spherocytosis
• Congenital dyserythropoietic anemia
• Pure red cell aplasias
TRANSFUSION DEPENDANT ANEMIA - OTHER INVESTIGATIONS

- Parents CBC and HPLC - normal
- Osmotic fragility test in parents - normal
- G6PD enzyme levels - normal
BONE MARROW ASPIRATE

Erythroid precursor

Erythroid precursors relatively less than myeloid cells
Bony trabeculae enclosing marrow particles with myeloid series and less erythroid series.
BONE MARROW BIOPSY

GLYCOPHORIN

No erythroid series seen

MYELOPEROXIDASE

Numerous myeloid cells seen
BONE MARROW BIOPSY - RETICULIN STAIN

Marrow fibrosis
• Parvo virus IgG - 50.7 NTU (positive)

Reference values: 
<9 NTU - negative
9-11 NTU - equivocal
>11 NTU - positive
FINAL DIAGNOSIS AND TREATMENT

Pure red cell aplasia

Congenital?

or

Acquired?

Prednisolone 2mg/kg/day P/O BD
DISCUSSION
DIAMOND BLACKFAN ANAEMIA

• Congenital pure red cell aplasia/Congenital hypoplastic anaemia

**ETIOLOGY:**
• Genetic/RPS19/AD inheritance
• Defective ribosome biosynthesis
• Apoptosis of erythroid progenitor cells
CLINICAL FEATURES

- MEDIAN AGE AT PRESENTATION: 2 months
- MEDIAN AGE AT DIAGNOSIS: 3-4 months
- Often symptomatic early in infancy (90% < 1yr)
- LBW
- Pallor at birth
- Non immune Hydrops fetalis
- Growth retardation
- Short stature
- Learning disabilities
- **CRANIOFACIAL:**
  - Hypertelorism
  - Broad, flat nasal bridge
  - Cleft palate
  - High arched palate
  - Microcephaly
  - Micrognathia
  - Microtia
  - Low set ears
  - Low hair line
  - Epicanthus
  - Ptosis

- **EYE:**
  - Congenital glaucoma
  - Strabismus
  - Congenital cataract

- **NECK:**
  - Short neck
  - Webbed neck
  - Sprengel deformity

- **THUMBS:**
  - Triphalyngeal
  - Duplex or bifid
  - Hypoplastic
  - Flat thenar eminence
  - Absent radial artery

- **UROGENITAL:**
  - Absent kidney
  - Horseshoe kidney
  - Hypospadias

- **CARDIAC:**
  - ASD, VSD, COA
DIAGNOSTIC CRITERIA:

1) Age <1yr
2) Macrocytic normochromic anaemia
3) Reticulocytopenia
4) Normocellular marrow with selective paucity of erythroid precursors

SUPPORTING CRITERIA:

Definitive/ not essential - DBA mutation
Major- positive family history
Minor- congenital abnormality, macrocytosis, increased Hb F, RBC deaminase activity.
TREATMENT

CORTICOSTEROIDS
Prednisolone 2mg/kg/day

TRANSFUSION THERAPY
Leukocyte irradiated packed RBC with iron chelators

HEMATOPOETIC STEM CELL TRANSPLANTATION
HLA matched sibling donor Tx
ALTERNATIVE THERAPIES

1) Androgens
2) High dose corticosteroids
3) Erythropoetin
4) Interlukin-3
5) Cyclosporine +/- Prednisolone
6) Metoclopromide
7) Valproic acid
8) Leucine
9) 6MP, Cyclophosphamide, Vincristine, Stem cell factor
10) Gene therapy - For RPS19 deficient DBA
Diagnosing and treating Diamond Blackfan anaemia: results of an international clinical consensus conference

Adrianna Vlachos,¹,² Sarah Ball,³ Niklas Dahl,⁴ Blanche P Alter,⁵ Sujit Sheth,⁶ Ugo Ramenghi,⁷ Joerg Meerpohl,⁶ Stefan Karlsson,⁹ Johnson M Liu,¹,² Thierry Leblanc,¹⁰ Carole Paley,¹¹ Elizabeth M Kang,¹² Eva Judmann Leder,¹ Eva Atsidaftos,² Akiko Shimamura,¹³ Monica Bessler,¹⁴ Bertil Glader,¹⁵ and Jeffrey M Lipton¹,², the participants of the Sixth Annual Daniella Maria Arturi International Consensus Conference

28 pts among more than 700 in literature- developed cancers

Acute leukemia-11
Myelodysplastic syndrome-3
Sarcoma-6
HL/NHL-3/1
Breast ca-2
HCC-2
Ca colon, stomach- 2
An Amish boy with cartilage-hair hypoplasia (CHH) and cell-mediated immunodeficiency developed “congenital” hypoplastic anemia (CHA) of the Diamond-Blackfan type by two months. Alterations of T cell function have been described separately in CHH and CHA, but this is the first known report linking the two conditions.
PARVOVIRUS & HEMATOPOIESIS

- Normal individuals - usually mild and self-limited bone marrow aplasia
- Hemolytic anemia - transient but severe anemia (aplastic crisis)
- Immunodeficient individuals - chronic parvovirus
CHRONIC PARVOVIRAL INFECTION - PRCA

• Occurs when the virus is not cleared by the immune system
  • HIV infection
  • Immunosuppressive drugs
  • Primary immunodeficiency
  • Rarely in immuno-competent
• Responds to immunoglobulin therapy
24 year - transfusion dependent anemia since 11 months of age
Diagnosed as DBA
Had hypogammaglobulinemia & G6PD deficiency
Diagnosis revised - Parvoviral serology & BM positivity for Parvoviral antigen by IHC
Response to IVIG+

American Journal of Hematology 2005
Pale pink intracellular inclusions in erythroid precursors (arrows)

Immunohistochemical staining for VP2 structural protein of parvovirus

American Journal of Hematology 2005
Congenital anaemia after transplacental B19 parvovirus infection

K.E. Brown, MRCP, S.W. Green, BS, J. Antunez de Mayolo, MD, N.S. Young, MD, J.A. Bellanti, MD, S.D. Smith, MD, T.J. Smith, MD

Abstract

We report three children with congenital anaemia after intrauterine infection with B19 parvovirus. All the fetuses developed hydrops fetalis that was treated by blood transfusion. After delivery the infants had hypogammaglobulinaemia. In all three, sera lacked B19 but viral DNA was found in bone marrow. All were treated with immunoglobulin. One child died and B19 was found in various tissues. In the other two cases, virus could no longer be detected after therapy but the patients remain persistently anaemic. Persistent B19 infection should be suspected in infants with congenital red-cell aplasia.
FUTURE PLAN OF INVESTIGATIONS

• Bone marrow IHC for parvoviral antigen
• Parvo-viral Blood PCR
• Mutation studies for Diamond Blackfan Anemia
1) **Pure red cell aplasia** Paul Fisch¹, Rupert Handgretinger² and Hans-Eckart Schaefer¹. Article first published online: 2 AUG 2008

2) **Persistent pure red cell aplasia in dicygotic twins with persistent congenital parvovirus B19 infection-remission following high dose intravenous immunoglobulin.** Lejeune A¹, Cremer M, von Bemuth H, Edelmann A, Modrow S, Bührer C.

3) **Recurrent severe anaemia: a rare presentation of parvovirus b19 infection.** Singh S¹, Chand G², Charan S³, Arora S⁴, Singh P⁵.

4) **Pure red cell aplasia in a three-months-old infant possibly secondary to cytomegalovirus infection.** Nandan D¹, Jahan A², Dewan V², Singh S³, Buxi G⁴.

5) **Congenital anaemia after transplacental B19 parvovirus infection** K.E Brown, MRC P, S.W Green, BS, J Antunez de Mayolo, MD, N.S Young, MD, J.A Bellanti, MD, S.D Smith, MD, Tj Smith, MD.
ACKNOWLEDGEMENT

BABY's PARENTS

NEONATOLOGY
Dr. Binu Ninan

PATHOLOGY
Dr. Febe

ENDOCRINOLOGY

PHO
Dr. Latha

NUTRITION
THANK YOU