What is DBA?

an inherited bone marrow failure syndrome

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(b) Hemoglobin
Diamond Blackfan Anaemia

- Hypoplastic macrocytic anaemia in infancy (lack of erythroid precursors in BM): 92% in first year of life
- eADA elevated in up to 85% cases
- 30% short stature
- Physical abnormalities:
  - Triphalangeal thumb, flattened thenar muscles, absent thumb
  - Cleft palate and other midline abnormalities
  - Cardiac abnormalities 15-20%
  - Renal abnormalities 15-20%
- Progression to other cytopenias/complete aplasia
- Cancer risk
Transient erythroblastopenia of childhood (TEC)

- Comparison with DBA:
  - 5/million/year
  - 85% 1 - 4 year at diagnosis
  - 50% have preceding viral illness
  - normal Hb F
  - normal ADA levels
  - usually in 4-8 weeks

Parvovirus B19
Exclude by PCR in BM
May last for several months and require several doses of IVIG
Age at presentation

- FA: 6.5 yr
- DC: 14 yr
- DBA: 3 mo
- SDS: 2 wk
Survival of patients with inherited bone marrow failure syndromes

Shimamura, 2009
DNA → Replication
           ↓  Transcription  
RNA       ↓  Translation  
           ↓              
protein
5 ribosomes reading same RNA sequentially

(Initiator codon)

AUG

5' Growing polypeptide chains

50S

UAG

Stop codon

Ribosome movement

5' mRNA

3' mRNA

Complete polypeptide

tRNA

30S
DBA is caused by mutations in genes affecting ribosomal function

Confirmed mutations are found in 11 of 80 ribosomal protein genes
5 to 7 per one million live births

53% families:
- RPS19 25%
- RPS24 2%
- RPS17 1%
- RPS7 1%
- RPL35a 3.4%
- RPL11 4.8%
- RPL5 6.6%
- RPS10 2.6%
- RPS26 6.4%
Diagnosis

- Often difficult unless someone else affected in the family
- Anaemia with high MCV and HbF
- ADA level increased

- Genetic analysis
eADA is increased and segregates in DBA

<table>
<thead>
<tr>
<th>Genetic Haplotype Within the Family</th>
<th>Same as DBA Case</th>
<th>Different From DBA Case</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>eADA</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Increased*</td>
<td>14</td>
<td>1</td>
<td>15</td>
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<tr>
<td>Normal</td>
<td>3</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>17</td>
<td>34</td>
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</tbody>
</table>
Physical features

Craniofacial features
- Cathie face
- High arched palate
- Cleft palate and lip
- Microcephaly

Cardiac anomalies
- Ventricular septal defect
- Atrial septal defect
- Coarctation of the aorta
- Complex cardiac anomalies

Ophthalmological
- Congenital glaucoma
- Strabismus
- Congenital cataract

Neck
- Short neck
- Webbed neck
- Sprengel deformity
- Klippel-Feil deformity

Hand thumb anomalies
- Hypoplastic thumbs
- Triphalyngeal
- Absent thumbs
- Thenar hypoplasia

Growth
- Growth retardation
- Osteoporosis

Urogenital anomalies
- Absent kidney
- Horseshoe kidney
- Hypospadias

Development
- Learning difficulties
- Behavioural difficulties
Risk of cancer

- Increased but not as much as other inherited bone marrow failure syndromes
- Risk approximately 5%
- If it occurs often at a younger age than the general population
- Any type, but there is an increase in leukaemia (AML), myelodysplasia and bone osteosarcoma

- Healthy lifestyle and good diet
- Not smoking and alcohol binge
- Use of sunscreen creams
- Avoid use of growth hormone
Diamond Blackfan Anaemia: summary of treatment status

transfusion independent
n=40 (60%)

transfusion dependent
n=27 (40%)
Steroids

• Avoid steroids until > 1 year
  – unless venous access limiting and Port-a-Cath needed
  – immunise against chickenpox before starting
  – post MMR vaccination

• Prednisolone 2 mg/kg/day for 4 weeks
  – reduce to 2 mg/kg alternate day over 8 weeks
  – then very slow reduction on alternate day dosage to find minimum maintenance dose
  – overshooting by coming down too fast may mean starting again at 2 mg/kg

• 0.5 mg/kg on alternate days
• Avoid increasing steroids in response to acute drop in haemoglobin associated with infection – use transfusion instead
initial treatment with steroids

- response
  - steroid independent
  - steroid dependent
  - become refractory
- no response
  - never TI
  - spontaneous remission

transfusion dependent
Transfusion Therapy

- Every three to four weeks
- Hb level individualised

Problems:
- disruption to normal activities
- vascular access
- iron load
- antibody formation

Chelation treatment
Osteoporosis may be increased:
  · Monitor 25 OH vitamin D and supplement with colecalciferol

Some patients associated deficiency of cellular or humoral immunity:
  · Prophylactic antibiotics
  · Monitor lung function tests and HR CT if abnormal
  · IVIG

Difficulty in feeding

Learning difficulties
Stem Cell Transplantation

• **Aim:**
  1. Eradicate the condition to be treated = achieve myeloablation
  2. Avoid rejection of the new bone marrow = avoid graft failure
  3. Avoid the body being attacked by the immune system derived from the new bone marrow = avoid Graft versus Host Disease

• **How is it achieved?**
  1. HLA matching
  2. Myeloablation
  3. Immunosuppression
Related bone marrow transplant:
  · Transfusion dependent children

Unrelated bone marrow transplant:
  · additional cytopenias
  · transformation
  · Impossibility to control iron load

Shlomchik, Nat Rev Immunol 2007
Inheritance

- Autosomal dominant