The Joys of Living with DBA (Diamond Blackfan Anaemia)

By Helen Witham

What is DBA?

- Diamond Blackfan Anaemia (congential Pure Red Cell Aplasia) is a rare bone marrow failure disorder
- DBA patients fail to produce red blood cells
- DBA affects males and females and all ethnicities equally
- The incidence of DBA is around 1 in 200000 live births;

History

- DBA was first recognised in 1936 by Hugh Josephs and then more completely described by L.K.Diamond and K.D. Blackfan in 1938
- The first DBA gene, Ribosomal Protein (RP) S19, was identified in 1999
- RPS19 is mutated in about 25% of DBA patients
- Mutations in an increasing number of other genes encoding RPs of the small (RPS24,RPS17,RPS7,RPS10,RPS26) and large (RPL5, RPL11,RPL35A) ribosomal subunits have also been described in DBA patients

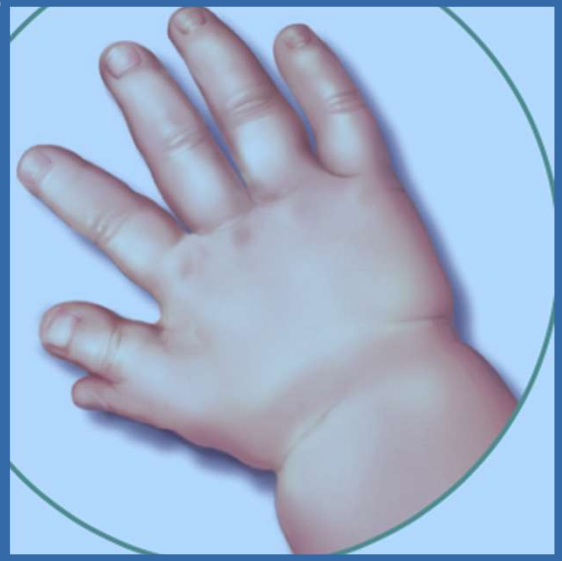
Pathophysiology

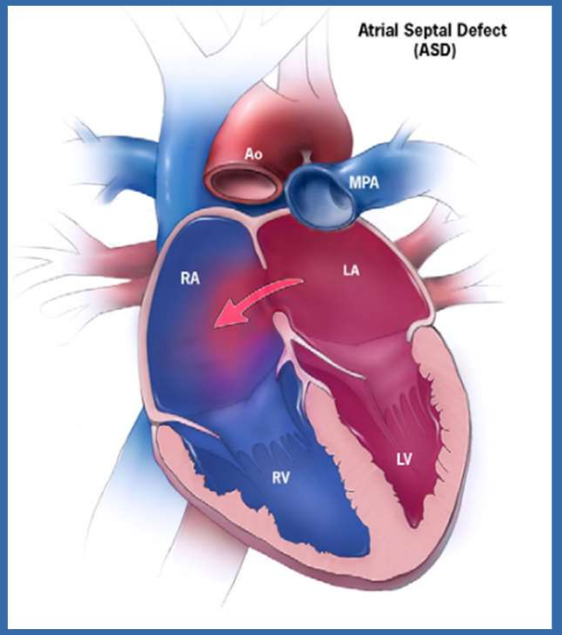
- DBA is one of the few diseases known to be caused by a defect in ribosomal proteins
- The genes in DBA all encode ribosomal proteins in either the RPS (small) or RPL (large) subunit
- Faulty ribosome biogenesis results in pro-apoptotic erythropoiesis leading to erythroid failure
- It is a genetically and clinically heterogenous disorder characterised by erythroid failure, congenital anomalies and a predisposition to cancer

Diagnosis of DBA

- Generally diagnosed within the first 12 months of life
- Severe anaemia (Hb < 70 g/L)
- Macrocytic cells
- Reticulocytopenia
- Normal or slightly decreased WBC's and platelets
- Normal bone marrow cellularity but with selective decrease in red blood cell precursors
- Increased Erythrocyte Adenosine Deaminase Activity (eADA) and Haemoglobin F

Congenital anomalies

- 
- genitourinary
- gastrointestinal anomalies
- Craniofacial anomalies



My Initial Presentation

- I was born after a normal pregnancy and delivery
- I weighed 6lbs 9oz
- Initial neonatal period was uneventful
- Increasing pallor during the first months of life

My DBA Diagnosis

- My haemoglobin was 40 g/L
- I had no other anomalies on clinical examination e.g. normal thumbs
- Bonemarrow aspiration showed a cellular marrow with a marked paucity of erythroid precursors
- Myeloid erythroid ratio was 50 to 1
- Some developing erythroid did have pyknotic and bizarre nuclei
- No evidence of Megaloblastic changes

The DBA Journey Begins

- Corticosteroids (prednisolone)
- Red Cell Transfusions

The Journey through the Early Years

- Monthly visits to the haematology clinic
- Endocrinology team for my height
- Cardiology team for a very loud heart murmur
- Hospital dentist for poor development of teeth
- ENT for swallowing difficulties

Childhood

- I made good developmental and growth progress although I had ups and downs with my blood
- At 2 years old I stopped responding to steroids and required transfusions but then responded again
- My height and weight at 5 years old remained below the 3rd percentile for my age
- Continued to respond to steroids which maintained my Hb between 80 - 90 g/L

Viral Infections

- Vaccinated when I was 13 years old but had reduced doses of all vaccines
- Unsure how my immune system would respond to vaccinations
- Teachers asked to inform my parents of any viral infection - chickenpox, measles, mumps
- When I came into contact with these childhood illnesses I would have to be injected with immunoglobulin

A spot of Measles

- I contracted measles at 10 years
- I was very unwell for about 3 months
- I stopped responding therapeutically to high dose steroids
- My bone marrow stopped producing all cells - Red cells, white cells and platelets

Early Adulthood

- Osteoporosis diagnosed at around 18 years
- Started on bisphosphonates - including Didronel, Fosamax, Pamidronate and Zoledronate; slow down bone turnover
- Fosamax caused ulceration of oesophagus
- Continued to respond to steroids with occasional high dose steroids due to infection or just because

Going viral at 32

- Contracted virus which had life changing effects
- Bonemarrow stopped responding to steroids and I became transfusion dependant
- Hb dropped to 45 g/L and I was transfused 3 units of packed red cells
- I did not respond to steroids again after the transfusion like I had in the past
- Developed DVT after 3 units of blood

Vicious Varicella

- Chickenpox contracted at 34 years old
- Covered in spots from the top of my head to the soles of my feet and inside my throat and urinary tract - ☹
- I was started on acyclovir and given zoster immunoglobulin
- I also had neuralgia - sharp stabbing pain in my knee
- Required more units of blood before returning to regular transfusion regime

Side effects of Steroids

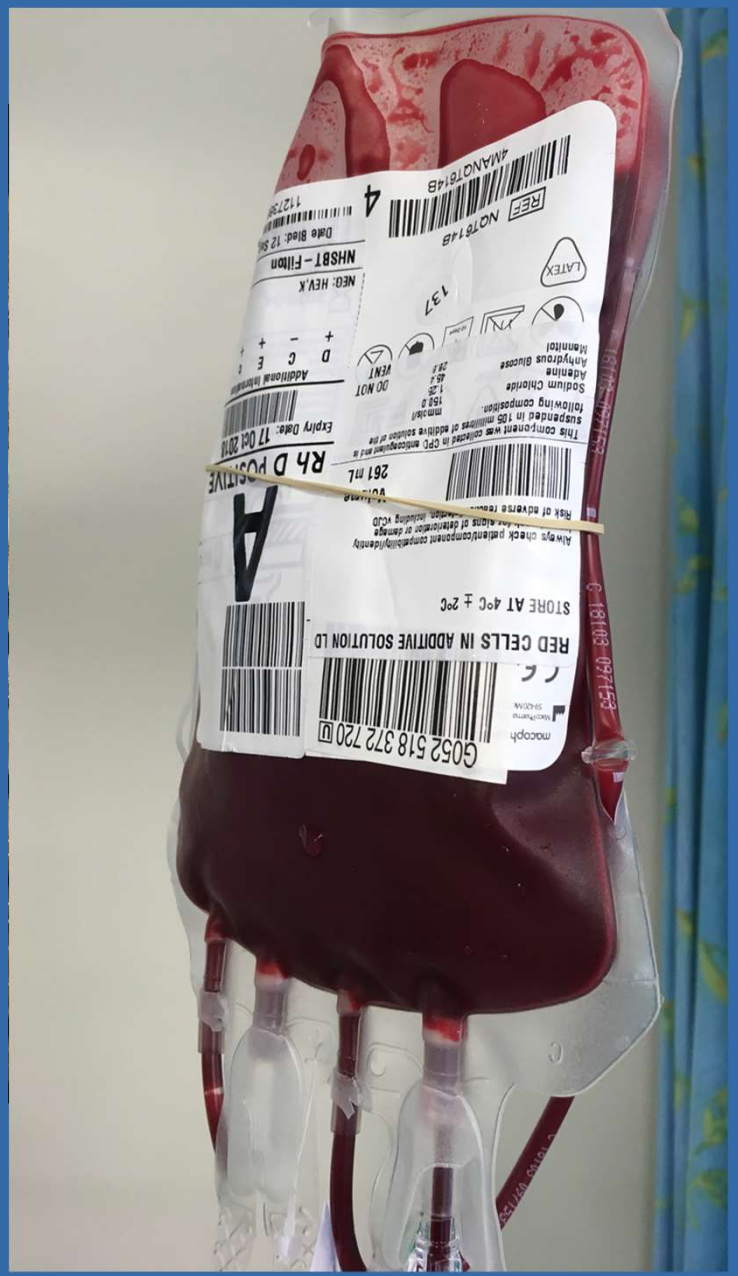
- Stunted growth
- Osteoporosis
- Immunocompromised
- Cataracts, Glaucoma, Diabetes

Anaemia

- My symptoms: fatigue, breathlessness on exertion, racing heart, nausea, headaches
- I can get irritable with everything becoming an effort
- Can function at a lower Hb as body seems to compensate and I adjust my activity level as Hb decreases

Pre Transfusion

- Generally transfused when Hb is in the 70's g/L



Transfusion Process

- I generally receive a blood transfusion in the oncology/haematology day unit - 2 units every 2 to 3 months
- Before the blood is administered I must confirm my name and DOB
- Two qualified nurses confirm all details on unit of blood match my hospital wrist band and double check number on unit matches paperwork
- Clinical observations include blood pressure, temperature and pulse are recorded before each unit is administered and 15 minutes after it has started

Administration of Blood

Each unit is transfused
via a pump over 2 hours

Post Transfusion

- Hb depends on characteristics of the blood received
- After a nights sleep I feel very well
- Not pale anymore
- Breathlessness upon exertion (within reason) disappears
- Increased energy
- Headaches and nausea disappear
- Heart does not feel like it is racing

Iron Chelation

- Body does not remove excess iron so I take a chelator called Exjade
- Exjade (deferasirox) is an orally active chelator that is highly selective for iron with a low affinity for zinc and copper
- It removes the iron that builds up in the body from the blood transfusions
- It binds iron with a high affinity in a 2:1 ratio
- Exjade promotes excretion of iron, primarily in the faeces
- Common side effects include diarrhoea, vomiting, nausea

Right now

- Do not have osteoporosis (bone density score for hip and spine is at the low end of normal)
- 50% chance of children also having DBA
- Work full time including shifts
- walk, swim and ski

Treatment for newly diagnosed DBA patients

- Infants diagnosed with DBA transfused for the first year
- Tube fed if required
- Vaccinated in the first year
- A Steroid Trial is started after the 1st year of transfusions
- If the Hb concentration remains above 90 g/L on a low dose of steroids (0.3mg/KG) - child is steroid responsive
- If non responsive the child returns to a transfusion regime

- Transfusion dependant DBA patients will be transfused every 3 to 4 weeks
- Transfused to a Hb of 130 g/L -140 g/L
- Do not let Hb go below 90 g/L
- Chelation therapy started at 2 years old
- Bone marrow transplant considered for children who do not tolerate transfusions and/or chelation therapy
- Bone marrow transplantation has a better success rate when performed before 10th birthday

My Future

- Change my transfusion regime and start having blood when my Hb is in the 90's g/L instead of the 70's g/L
- T2-Ferriscan to measure cardiac iron levels
- Genetic screening against the known gene mutations seen in DBA to identify RPS or RPL subunit mutation

The Future of DBA

- Research using zebrafish to further understand the pathophysiology of DBA - the cause of 40 -50 % of DBA cases are unknown
- More research required to understand why glucocorticoids work - reason still unknown
- Find new treatments (drugs) and possibly a cure

References

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