The Joys of Living with DBA (Diamond Blackfan Anaemia)

By Helen Witham
What is DBA?

- Diamond Blackfan Anaemia (congenital 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 heterogeneous 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
- Bone marrow 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
- Bone marrow 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

- diamondblackfan.org.uk

- Diamond Blackfan Anemia Registry - https:\www.dbar.org


- medicines.org.uk (Exjade, Novartis Pharmaceuticals)