Sickle cell disease management

Mike Richards
Paediatric Haematologist
Sickle cell anaemia

- Most common genetic condition in UK
  - Incidence 1:2000

- Autosomal recessive disorder

- Hydrophilic amino acid glutamic acid replaced with the hydrophobic amino acid valine at the sixth position of $\beta$-globin haemoglobin chain

- In low-oxygen conditions the change in amino acid structure promotes the non-covalent polymerisation of haemoglobin

- Distortion of red blood cells into a sickle shape and decreases their elasticity
Sickle haemoglobin polymerisation

Vasopathology of Sickle Cell Disease

- Sickle-RBC Adhesion
- Abnormal Shear
- Inflammation
- Oxidative endothelial cell damage (ROS)
- ↑ serum free hemoglobin (Hb)
- Dysregulation of nitric oxide pathway (NOS)
- ↑ Cell adhesion molecule (CAM) and tissue factor (TF) expression
- Loss of vasoregulation
- Intimal hyperplasia
- Platelet and leukocyte adhesion
- Propagation of fibrin clot
- Entrapment of rigid sickle RBCs
Sickling disorders

- HbSS
- HbSC
  - Increased risk of retinopathy and avascular necrosis of hip
- HbS trait/$\beta^0$-thalassaemia trait compound heterozygous state
- HbS trait/$\beta^+$/thalassaemia trait compound heterozygous state
- HbS/D$^{\text{Punjab}}$
- HbS/O$^{\text{Arab}}$
Clinical presentations of vaso-occlusion

- Neurocognitive impairment
- Cerebral infarcts
- Stroke
- Pulmonary infarcts
- Pneumonia
- Splenomegaly
- Splenic atrophy (autosplenectomy)
- Retinopathy
- Congestive heart failure
- Cholelithiasis
- Renal infarcts
- Hematuria
- Bone marrow hyperplasia
- Aseptic bone necrosis
- Osteomyelitis
- Vaso-occlusion
- Ulcer
- Infarcts of the extremities
Specific organ damage in sickle cell disease

Kidney

- Glomerular hyperfiltration, hyposthenuria, asymptomatic microalbuminuria

- Focal segmental glomerulosclerosis

- End-stage renal disease occurs in up to 30% of adults

- At a mean age of 13 months 23% of infants were unable to concentrate urine with controlled fluid deprivation
Specific organ damage in sickle cell disease

Lungs

- 90% of adults with sickle cell disease have abnormal lung function

- Children have demonstrated a progressive decline in lung volumes with early lower airway obstruction, restriction, and airway hyper-reactivity
Specific organ damage in sickle cell disease

Brain

- Cerebro-vascular events such as overt strokes occur in 24% cases by the age of 45 years

- Silent cerebral infarcts, high-signal MRI abnormalities in the absence of overt neurological signs detectable in 20% - 35% of children

- Silent cerebral infarcts in 13% cases at a median age of 13.7 months
Specific organ damage in sickle cell disease

Spleen

- 88% of young children had decreased or absent splenic uptake

- Associated increased risk of overwhelming encapsulated organism infection
Sickle cell prognosis

- Modern life expectancy of patient with homozygous sickle cell disease in Europe/North America is 53-60 years

- Potential risk factors for adverse outcomes
  (not validated in recent studies)
  - lower Hb
  - lower HbF
  - higher white cell count
  - early dactylitis
Aims of sickle-cell modulating therapy

- Reduce the frequency of vaso-occlusive crises
- Slow or halt long term organ damage
Potted history of sickle cell management

1922
Sickle cell anaemia
first named by Verne Mason

1949
‘Sickle cell anemia – a molecular disorder’
Linus Pauling

1982
Questionable evidence for folate supplementation

1984
First stem cell transplant for Sickle cell patient (with AML)

1986
PROPS
Regular penicillin prophylaxis recommended (84% Reduced incidence of infection)

1986
Adult trial of Hydroxycarbamide

1983
Questionable evidence for folate supplementation

1984
First stem cell transplant for Sickle cell patient (with AML)

1986
PROPS
Regular penicillin prophylaxis recommended (84% Reduced incidence of infection)

1988
STOP
Stroke prevention by transfusion study

2001
Introduction of NHS Sickle Cell and Thalassaemia Neonatal Screening Programme*

2011
Baby HUG trial Hydroxycarbamide in children
Hydroxycarbamide

- Antineoplastic drug that inhibits ribonucleotide reductase in DNA synthesis used in myeloproliferative disorders

- Hydroxycarbamide induced marrow suppression leads to
  - proliferation of RBC precursors containing HbF
  - haemoglobin content is increased
  - increased sickle RBC hydration
  - reduction of RBC adherence to endothelial cells
  - improved nitric oxide metabolism

- 1996 double-blinded placebo-controlled study in adults with severe sickle cell disease hydroxycarbamide substantially reduced
  - episodes of pain and acute chest syndrome
  - hospital admissions
  - transfusions
BABY-HUG
Winfred C Wang et al
Lancet 2011

- Randomised controlled double blinded trial

- Inclusion criteria
  - sickle cell disease of all severity
  - age 9 – 18 months
  - 193 subjects randomised

- Hydroxycarbamide (20 mg/kg/day fixed dose) or placebo for two years

- Treatment group comparisons were by intention-to-treat analysis
Cumulative probability curves of time to first event for acute chest syndrome, pain, dactylitis and transfusion.
Results – organ function

- Secondary measures of spleen, kidney, and central nervous system function suggested benefit, but these results were not significant.

- Significant increased total haemoglobin and foetal haemoglobin and lower WBC counts.

- No excess or novel toxicities.

- Poorly characterised toxicities – leukaemogenesis and impaired fertility.
Indications for Hydroxycarbamide use in UK

Main
- ≥ 3 admissions for painful episodes in previous 12 months
- > 1 admission with painful crisis in previous 12 months & symptomatic in community
- Two or more episodes of acute chest syndrome in the last 2 years, or one episode requiring ventilatory support

Other
- Chronic symptomatic anaemia
- Priapism
- Nephropathy
- Pulmonary hypertension

But should we use more liberally? Probably yes
Prophylactic red cell transfusions for prevention of sickle stroke

- STOP study (Stroke Prevention Trial in Sickle Cell Anemia) Adams et al 1998
- Prophylactic red-cell transfusions in children identified by transcranial Doppler ultrasonography as at high risk for stroke
- Incidence of stroke decreased from 10% per annum to <1% per annum
- But risks of chronic transfusions
  - Iron loading
  - Alloantibody formation
  - Infection
  - Hospital attendance
Transcranial Doppler Probe
Can you stop the transfusions?

- STOP 2 study (Optimizing Primary Stroke Prevention in Sickle Cell Anemia) Adams et al 2005

- Inclusion criteria: Patients on prophylactic transfusions for >30 months for high risk TCD who had reduced blood flow velocity to normal

- Randomised to continue transfusions or discontinue

- 41 children stopped transfusion
  High-risk Doppler results developed in 14 and stroke in 2 others within a mean (±SD) of 4.5 ± 2.6 months of the last transfusion

- 38 children continued transfusion
  No adverse events
Stem cell transplant

The British Paediatric Haematology Forum
Recommendations

Indications
- <17 years with HLA-identical sibling and informed consent
- One or more of these SCD-related complications:
  - CNS disease
  - Recurrent acute chest syndrome
  - Stage I/II chronic sickle lung disease
  - Recurrent, severe, debilitating pain (>3 hospital admissions/year in 3-4 years)
  - Problems relating to future care – to be decided on case-by-case basis

Exclusions
- Donor with a major haemoglobinopathy
- One or more of the following:
  - Karnofsky performance <70%
  - Portal fibrosis (moderate or severe)
  - Renal failure (GFR <30%)
  - Major intellectual impairment
  - Stage III or IV chronic sickle lung disease
  - Cardiomyopathy
  - HIV infection
The clinical course of a patient with sickle cell disease

- 8 yrs old boy
  - Family from the Ivory Coast
  - SS disease diagnosed at neonatal screening
  - Hb 70-90 g/L
  - HbF 12%
  - White cell count 13 x10^9/l

- 14mnths to 6 yrs
  - 7 hospital admissions for infection
  - 3 for painful crises

- 5 yrs March 2011
  - Started monthly red cell transfusions

- January 2012
  - V max
  - Right MCA 190-213 cm/sec
  - Restarted monthly red cell transfusions

- February 2012
  - No HLA matched bone marrow donor available so started Hydroxycarbamide

- 0 - 14 months
  - 3 episodes of dactylitis

- 5 years
  - Transcranial Doppler scanning in Leeds
  - V max left MCA
    - 1. 180 cm/sec
    - 2. 162-180 cm/sec

- July 2011
  - Positive Direct Agglutination Test so transfusion programme arrested

- February 2012
  - Red cell alloantibodies detected: Anti Fy^a, Fy^b, S, Ce, Kell
  - Transfusions abandoned

- April 2014
  - Asymptomatic
  - V max 167 cm/sec
  - Hydroxycarbamide 30mg/kg
  - No side effects
Maximum velocity of cerebral blood flow and interventions

- Monthly blood transfusion programs
- Hydroxycarbamide treatment
  Escalating dose

Graph showing the maximum velocity (V max) of cerebral blood flow in cm/sec over time from 01/02/2011 to 01/12/2013.
Magnetic Resonance Angiogram
Magnetic Resonance
Digital Subtraction Angiogram
Sickle Cell Disease
Potential novel therapies
Pathophysiology of sickle cell organ injury

RBC membrane injury exposes phosphatidylserine and haemoglobin release → Nitric oxide (NO) deficiency → Increased RBC adherence to the endothelium, impaired blood flow → Ischaemia reperfusion injury, increase in cytokines and activation of leukocytes, procoagulants and adhesion molecules

Cytoprotective mediators such as antioxidants are depleted

Ineffective erythropoiesis partly secondary to functional iron deficiency caused by inadequate circulating transferrin
Sickle Cell Disease
Potential novel therapies

Inhibitors of cellular adhesion (phase 1 and 2 trials)
- GMI-1070, a pan-selectin inhibitor
- Heparin
- Eptifibatide, platelet antagonist
- Propanolol

Anti inflammatories (phase 1 trial)
- Regadenoson A_2A_ R agonist that blocks iNKT cell activation
- Statins
- Zileuton 5-lipoxygenase inhibitor that decreases inflammation
- MP4CO A haemoglobin conjugated with polyethylene glycol and saturated with carbon monoxide

NO-arginine dysregulation (phase 1,2,3 trials)
- L-arginine Substrate of NO that increases NO synthesis
- Tetrahydrobiopterin (R-BH4) Essential cofactor for NO production
- Nitrite, niacin NO donor
Sickle Cell Disease
Potential novel therapies

Oxidative injury (phase 3 trials)
■ Oral supplementation of glutamine in SCD

Iron metabolism and erythropoiesis (animal models)
■ Transferrin injections
■ Jak-2 inhibitors
Sickle cell management - summary

- Previously reactive care to crises
- Last decade exciting new advances to provide primary prevention strategies
- Still need new interventions to intervene in acute crisis
- Possible increasing roles for hydroxycarbamide and stem cell transplant
Haemolytic state

- Shortened half life of red cells
- Compensatory reticulocytosis
- Hyperbilirubinaemia
- Elevated LDH, reduced haptoglobin
- Functional deficiency of nitric oxide
  - Vascular endothelial damage
Potential complications

- Haemolytic state
  - Increased rate of haemolysis
    - Infection
  - Reduced rate of red cell production
    - Virus infection
    - Haematinic deficiency
- Splenic pathology
  - Increased consumption
  - Reduced splenic function
- Bile pigment gall stones
Potential complications

- Vaso-occlusive complications
  - Site specific
    - Limbs/skeleton
      - Pain, swelling, heat, bone infarction
      - Dactylitis in infants, stunted digit growth
    - Chest
      - Pain, hypoxia +/- secondary infection
    - Abdomen
      - Pain, ileus
    - CNS
      - Stroke/TIA
    - Priapism
Potential complications

- **Vaso-occlusive complications**
  - **Splenic infarction**
    - Overwhelming post splenectomy infection
    - Rationale for national newborn screening program
  - **Splenic sequestration**
    - Rapidly enlarging spleen
    - Life threatening anaemia
  - **Hepatic sequestration**
    - Rapidly enlarging liver
    - Liver dysfunction
Potential complications

- Vaso-occlusive complications
  - Ophthalmic
    - Proliferative retinopathy
    - Potential vitreous haemorrhage