Pulmonary complications of sickle cell disease - is prevention in sight?

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Sickle Cell Disease (SCD)

- It is the commonest inherited disorder in African and Caribbean populations; also occurs in the Middle East, Greece and India

- 200 million carriers of sickle cell trait

- 200-250 thousand children are born each year with SCD
Pulmonary complications of SCD

• Sickle chronic lung disease (SCLD) and acute chest syndrome (ACS) - leading causes of premature death

• Fatal pulmonary complications occur in 20% of adults

• Life expectancy is 48 years for women and 42 years from men for HbSS
Sickle Chronic Lung Disease

• Occurs in 4% of patients

• Hypoxaemia, restrictive lung disease, cor pulmonale and on CXR diffuse interstitial abnormalities; one third develop pulmonary hypertension

• No curative treatment

• Recurrence of ACS predisposes to SCLD
**Acute Chest Syndrome**

- Fever and cough are more common in the very young and chest pain, SOB and hemoptysis with advancing age
- A new pulmonary opacity on the CXR is essential to the diagnosis
- More common in children
- 50% will have had an ACS by 10 years of age
- Approximately 10-15% will require IPPV
- High haemoglobin levels predispose to ACS
- Inversely proportional to HbF levels
Treatment of ACS episodes

- Broad spectrum antibiotics (including treatment of atypical organisms)
- Oxygen (blood gases rather than oximetry)
- Careful rehydration
- Transfusion
- Analgesia
- Incentive spirometry
- iNO
Treatment of SCD complications

- Improve oxyhaemoglobin saturation
- Simple and exchange transfusion, decrease HbS and improve oxygen carrying capacity
- Aggressive chronic transfusion reduced ACS incidence

  Miller et al (STOP) J Pediatr 2001

- Hydroxyurea increases HbF and hence reduces HbS levels
- Reduced rates of ACS, VOC and hospitalisation

  Charache et al NEJM 1995
Lung function decline with age in SCD children

Sylvester et al Thorax 2004
Total lung capacity

Cohort 1
Mean change = - 4.73% per year
p = 0.0090

Cohort 2
Mean change = - 1.55% per year
P<0.0001
Asthma and ACS

• Increased inflammatory mediators and vascular leak during an ACS could result in chronic AHR and asthma

OR

• During an acute asthma episode:
  - inflammatory mediators and oxidant species could increase adhesion molecules and erythrocytes adhere to the vascular endothelium - vascular occlusive crisis.
  - in addition, hypoxia during an acute asthma episode would promote sickling
UK and Jamaican SCD children

- UK - of 165 children (0.3-17 years old, 151 controls)
  - 11% asthma
  - 33 (20%) had an ACS episode

- Jamaica - of 80 children (5-10 years, 80 controls)
  - 48% asthma
  - 41 (51%) had 66 ACS episodes
    (maximum 6)
Jamaican children

<table>
<thead>
<tr>
<th></th>
<th>SCD</th>
<th>Controls</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Asthma ever</td>
<td>48%</td>
<td>22%</td>
<td>0.02</td>
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<tr>
<td>Current asthma</td>
<td>41%</td>
<td>15%</td>
<td>0.001</td>
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<tr>
<td>atopic</td>
<td>19%</td>
<td>6%</td>
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<tr>
<td>non-atopic</td>
<td>22%</td>
<td>9%</td>
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<tr>
<td>Atopy</td>
<td>36%</td>
<td>34%</td>
<td>0.75</td>
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<tr>
<td>Airway responsiveness</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>44%</td>
<td>20%</td>
<td>0.02</td>
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</tbody>
</table>

Knight-Madden et al Thorax 2005
Temporal relationship of asthma and ACS

Anti-asthma medication:
• 12 of 165 SCD children
• 14 of 151 controls
  \[ p = 0.7 \]
• 7 of 33 ACS
• 9 of 132 non ACS
  \[ p = 0.0313 \]
• Asthma diagnosed median 1.3 (0.5-7) years before the first ACS episode

Sylvester et al Ped Pulmonol 2006
Mortality, asthma and smoking in young adults with SCD

• 75 SCD adults and 47 controls followed for a 10 year period
• Mortality rate 1.6 versus 0.2 per 100 patient years (p=0.03)
• Current asthma: hazard ratio 11.2 (2.5-50.6)
• Smoking: HR 2.7 (1.3-5.5)

Knight-Madden et al Lung et al 2013
Is all that wheezes asthma?

- Recurrent, severe wheezing regardless of an asthma diagnosis was associated with increased mortality and morbidity
  
  Cohen et al Am J Hematol 2011

- 19% of 262 patients attending ED had at least one episode of wheezing (only 50% had an asthma diagnosis)
  - those that had asthma more painful crises attendances
  - those with wheezing more attendances for painful crises and ACS episodes

Glassberg et al Br J Haematol 2012
Knight-Madden and Greenough Paed Rev 2014
Computed tomography and pulmonary function abnormalities

- 33 patients median 36 (range 17-67) years
- 18 patients had lung function abnormalities
- 30 had HRCT abnormalities; lobar volume loss, prominent central vessels, reticular/ground glass opacification (interstitial lung disease).
- All lung function results correlated with lobar volume loss on HRCT
- Reductions in FEV1 and FVC correlated with prominent central vessels

Sylvester et al ERJ 2006
Pulmonary function, CT and echocardiographic abnormalities

• 35 SCD adults 17-73 years (20 studied 6.6 years previously)

• Correlation between small vessel pulmonary vascular dimensions (pulmonary vascular volume), LFTs and echo estimates of ventricular function and cardiac output

• The decline in lung function correlated with changes in vascular dimension

Lunt et al Thorax 2014
Prospective study

- 45 children with SCD (HbSS) and 42 age, gender and ethnic-origin matched controls

- Respiratory system resistance measured by impulse oscillometry at 5Hz (R5, expressed as % predicted for height).

- Pulmonary capillary blood volume (corrected for lung volume) (Vc/VA) assessing using the carbon monoxide and nitric oxide single breath breath-hold technique.
Pulmonary capillary blood volume and oscillometric resistance at 5Hz

Wedderburn et al. Paed Pulmonol 2013
Lung function before and after transfusion

- **Vc/VA (m/l)**
  - Pre Tx: 20, 40, 60
  - Post Tx: 40, 60, 80
  - p = 0.0039

- **R5%pred (%)**
  - Pre Tx: 40, 60, 80
  - Post Tx: 60, 80, 100
  - p = 0.0020

- **FEV1%pred (%)**
  - Pre Tx: 60, 80, 100
  - Post Tx: 80, 100, 120
  - p = 0.0273

- **VC%pred (%)**
  - Pre Tx: 60, 80, 100
  - Post Tx: 80, 100, 120
  - p = 0.0195
Conclusions

- Respiratory function is worse even in young SCD children than ethnically matched controls.
- Restrictive abnormalities become more common with advancing age.
- Lung function is worst in those who have suffered recurrent ACS episodes.
- Asthma may predispose to ACS episodes.
- Lung function changes may reflect pulmonary vascular abnormalities which are due to chronic anaemia.
- Lung function decline is greatest in very young children when ACS episodes are most common, hence interventions need to be started early if they are to be most effective.
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