Do patients with sickle cell disease have asthma?

Anne Greenough
Faculty of Life Sciences and Medicine
King’s College, London
Sickle Cell Disease (SCD)

• Pulmonary complications are a major cause of morbidity and premature death

• SCD is the most common inherited disorder in African and Caribbean populations

• Life expectancy is 48 years for women and 42 years for men with HbSS.
ACS and asthma

- National Acute Chest Syndrome Study – 20% responded to bronchodilators

- What is the relationship of asthma to SCD pulmonary morbidity?
  - UK 165 SCD children (0.3 - 17.3 years) and 151 similarly aged ethnic matched controls
  - Jamaica – 80 children with SCD and 80 ethnic matched controls, aged five to ten years - modified version of the ISAAC questionnaire – “touch of” asthma
## Results

<table>
<thead>
<tr>
<th></th>
<th>SCD</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma ever</td>
<td>48%</td>
<td>22%</td>
<td>0.002</td>
</tr>
<tr>
<td>Current asthma</td>
<td>41%</td>
<td>15%</td>
<td>0.001</td>
</tr>
<tr>
<td>atopic</td>
<td>19%</td>
<td>6%</td>
<td>0.03</td>
</tr>
<tr>
<td>non-atopic</td>
<td>22%</td>
<td>9%</td>
<td>0.03</td>
</tr>
<tr>
<td>Atopy</td>
<td>36%</td>
<td>34%</td>
<td>0.75</td>
</tr>
<tr>
<td>Bronchodilator</td>
<td>14%</td>
<td>6%</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Knight-Madden et al. Thorax 2005
Jamaican and UK SCD children

• Jamaica - of 80 children
  - 48% asthma
  - 41 (51%) had 66 ACS episodes
  (maximum 6)

• UK - of 165 children
  - 11% asthma
  - 33 (20%) had an ACS episode
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
Asthma and SCD complications

- Amongst 1963 patients, asthma was associated with increased mortality (HR 2.36)
  
  Boyd et al Haematologica 2007

- Sibling history of asthma greater rate of pain episodes (RR 2.48)
  
  Field et al Am J Haematol 2008

- In French children asthma associated with increased ACS (RR 1.88) but not hospitalisation for pain
  
  Bernaudin et al Haematologica 2008

- In Saudi Arabia asthma associated with an increased ACS rate
  
  J Pediatr Hematol Oncol 2012

- Retrospective review of ACS inpatients, in HbSC versus HbSS asthma/wheezing was more common (51 vs 34%, p=0.041)
  
  Poulter et al Pediatr Blood Cancer 2011
Diagnosing asthma
Diagnosing asthma

Proposed definition of asthma:
• repetitive wheezing causing SOB or with exercise
• parental history of asthma
• two positive aeroallergen skin tests
• children aged over four years of age

Suspect asthma if ACS episodes occur without chest x-ray changes
Diagnosing asthma

• Incidence of airway hyper-responsiveness varies from 0 to 70%

• No consensus regarding which challenge should be used: metacholine, cold air or exercise

DeBaun and Strunk Lancet 2016
Perhaps it isn’t asthma?
Wheezing and asthma – independent risk factors for SCD morbidity

- Retrospective analysis of 262 ED visits for pain and ACS (ages 6 months to 67.5 years)
- 18.7% had at least one wheezing episode.
- 53% of patients with wheezing did not have an asthma diagnosis
- Wheezing was associated with a 118% increase in ED visits for pain and 158% for ACS
- Asthma 44% increase for pain and no increase for ACS

Glassberg et al Br J Haematol 2012
Wheezing in SCD

- 163 SCD children (8.5 years) and 96 controls (7.7 years) in Nigeria

<table>
<thead>
<tr>
<th></th>
<th>SCD</th>
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<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheezing:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with colds</td>
<td>17.3%</td>
<td>2.1%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>without colds</td>
<td>4.9%</td>
<td>0%</td>
<td>=0.03</td>
</tr>
<tr>
<td>Asthma</td>
<td>4.9%</td>
<td>1%</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Airways obstruction and FeNO

• 50 SCD children and 50 controls

• 14% SCD children and 24% of the controls had a doctor diagnosis of asthma

• Airways obstruction was higher in the SCD children (p=0.002), but not associated with increased metacholine sensitivity

• FeNO levels were similar in the two groups

Chaudry et al Thorax 2014
Exhaled nitric oxide

- Exhaled nitric oxide (FeNO) is elevated in asthma.
- FeNO is elevated in patients with atrial septal defects or liver cirrhosis.
- Both conditions are associated with a hyper-dynamic pulmonary circulation, which occurs in SCD.
- FeNO is correlated with increased pulmonary blood flow.


- To determine if airway NO and alveolar NO production differed between children with SCD and ethnic-matched controls and whether:
  - airway NO correlated with airways obstruction
  - alveolar NO correlated with a hyperdynamic pulmonary circulation.
## Results

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<th></th>
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</tr>
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<tbody>
<tr>
<td>n</td>
<td>18</td>
<td>n=18</td>
<td></td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>79.1(47.5-105.8)</td>
<td>104.5(78.6-124.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VC</td>
<td>85.1(48.6-107.8)</td>
<td>107.5(80.2-125.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FEF$_{25-75}$</td>
<td>58.5(29.2-138.2)</td>
<td>92.4(53.5-153.9)</td>
<td>0.0071</td>
</tr>
<tr>
<td>FEV$_1$:VC</td>
<td>91.0(75.2-104.5)</td>
<td>98.8(87.3-112.1)</td>
<td>0.0315</td>
</tr>
<tr>
<td>Rrs5</td>
<td>145.6(107.8-234.1)</td>
<td>111.7(67.2-168.6)</td>
<td>0.0008</td>
</tr>
</tbody>
</table>
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<td>18</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>FeNO,50ml/s</td>
<td>14.7(1.6-92.3)</td>
<td>14.6(1.2-56.1)</td>
<td>0.7569</td>
</tr>
<tr>
<td>J'_aw,NO</td>
<td>33.5(6.1-403.6)</td>
<td>60.8(1.4-319.1)</td>
<td>0.3038</td>
</tr>
<tr>
<td>CA,NO</td>
<td>7.0(1.3-7.3)</td>
<td>2.5(0.6-5.9)</td>
<td>0.0007</td>
</tr>
<tr>
<td>V'_A,NO</td>
<td>319.0(57.3-663.7)</td>
<td>151.0(31.8-447.1)</td>
<td>0.0224</td>
</tr>
<tr>
<td>Q_pulm</td>
<td>7.80(4.25-10.85)</td>
<td>5.50(3.55-7.70)</td>
<td>0.0006</td>
</tr>
<tr>
<td>QI_pulm</td>
<td>4.97(3.77-6.82)</td>
<td>3.29(2.48-4.50)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Alveolar nitric oxide production versus pulmonary blood flow index in the SCD children
If it is not asthma what is it?
Pulmonary capillary blood volume and oscillometric resistance at 5Hz

Wedderburn et al. Paed Pulmonol 2014
A pulmonary circulation - airway interaction?

Acute intravascular volume expansion in patients with heart failure increased airflow obstruction.

*Puri S, et al, Circulation 1999*

Intra-thoracic vascular volume expansion resulted in airway obstruction in asthmatics.

*Gilbert I et al, Clin Res 1990*

Raising intrathoracic blood volume using pneumatic trouser inflation increased airflow resistance in healthy subjects.

*Lorino AM, et al Euro Respir J 1994*
Pulmonary circulation - airway interaction?

- Not appropriate to perform fluid loading in SCD children.

But:

- Some SCD children receive blood transfusions as part of their routine care.

- This would allow investigation of the acute effect of fluid loading on lung function.
Subjects

- Eighteen subjects median age 14.2 (range 6.6-18.5) years
- Their median haemoglobin was 10.1 (range 8.2 – 11.6) g/dl.
- The median packed red cell volume (PRCV) administered was 500 (250 – 800) ml.
- Eight children (44%) had had at least one acute chest syndrome episode
- Four (22%) had a physician’s diagnosis of asthma.
Results
Results

• The change in pulmonary capillary blood volume correlated with the packed red cell volume (p=0.0152).

• The percentage change from baseline in pulmonary capillary blood volume correlated with the change in lung function (Rrs5) (p=0.04933).

Lunt et al Respir Physiol & Neurobiol 2015
What happens in the long term
Lung function decline with age in SCD children

Sylvester et al Thorax 2004
Longitudinal study

• Two cohorts of SCD children and ethnic matched controls prospectively followed
• 47 SCD and 26 controls median age 8.8 years and follow-up two years
• 45 SCD and 26 controls median age 10.2 years and follow-up of 10 years

Lunt et al Ped Pulmonol 2016
Total lung capacity
Longitudinal assessment of lung function

• The rate of decline was greater in the younger cohort who had more ACS episodes (12.6 versus 1.93 patient/years)

• The response to a bronchodilator challenge did not have a significant effect

• These results emphasise the need for more effective methods of preventing and treating ACS episodes

Lunt et al Ped Pulmonol 2016
Conclusions

- A physician diagnosis of asthma is associated with an increased risk of ACS episodes
- Obstructive lung function abnormalities also reflect pulmonary vascular abnormalities
- The diagnosis of asthma needs to be more robustly defined but metacholine challenges should not be used
- The role of anti-asthma medication overall in improving respiratory health of SCD children remains uncertain
- Whether an SCD child would benefit from anti-asthma therapy should be assessed on a case by case basis
Acknowledgements

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