Nocturnal oxygen saturation and painful sickle cell crises in children

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Abstract

The pathogenesis of acute painful crisis in children with sickle cell disease is poorly understood; suggested risk factors include sickle cell type, severity of anemia, fetal hemoglobin concentration and hypoxemia from upper airways obstruction. In a cohort study of 95 patients the relationship between clinical, laboratory and sleep study data and frequency of painful crisis was investigated. Both univariate and multiple regression modelling showed that low nocturnal oxygen saturation was highly significantly associated with a higher rate of painful crisis in childhood (p<0.0001). Screening and treatment for hypoxemia may reduce the frequency of this and other complications of the disease.

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Introduction

Painful crisis is the most common event in children with sickle cell disease (SCD) but the pathogenesis remains poorly understood. Acutely, precipitating factors may include cold, dehydration, infection, and hypoxia and there are epidemiological data suggesting that genotype, early dactylitis, leucocytosis, hemoglobin and hemoglobin F are risk factors for frequent pain.1-4

There is increasing evidence that pulse oximetry measurements in sickle cell disease reflect arterial oxygen saturation.5 Nocturnal desaturation, measured using pulse oximetry, is common in SCD, possibly secondary to upper airway obstruction (UAO).6-10 We have previously published the results of a cohort study investigating the relationship between nocturnal hypoxemia and central nervous morbidity;9 we present here the effect on pain as a secondary endpoint.

Participants and methods

The cohort of 95 patients attending the sickle cell clinic at the Queen Elizabeth Children’s Hospital in Hackney, London was studied from 1st January 1991 to 30th April 2000. The Hospital ethics committee approved the study and written informed consent was obtained. Painful crises requiring hospital treatment (emergency room and/or admission) were recorded. A pain rate (hospital days for pain/years of follow up) was calculated for the whole follow up period or until death (2 patients) or the initiation of regular transfusion (14 patients) or hydroxyurea (1 patient). Data were
recorded on risk factors previously reported in the literature\(^3,4\) including: dactylitis in the first year of life, mean hemoglobin (early Hb) and white blood cell count (early WBC) from the second year, baseline hemoglobin and hematocrit (Hb, Hct, at sleep study), fetal hemoglobin levels (HbF, only HbSS) and timing of adenotonsillectomy if performed.

A pulse oximeter (Ohmeda Biox 3700) was used to record oxygen saturation (\(\text{SaO}_2\)) continuously during sleep and the data were analysed blind to the pain data. Sixty-three sleep studies took place in the patients’ home; the remainder took place in the Sleep Laboratory at Great Ormond Street Hospital. Studies lasted from 4.3 to 8.2 (median 7.5) hours. Movement artefact was excluded manually. We examined the data for mean and minimum \(\text{SaO}_2\) and percentage of sleep spent at \(\text{SaO}_2 < 90\%\) and <80%. We also classified the sleep studies as with or without significant transient or prolonged dips (>4% from baseline) in oxygenation associated with acute pulse rate rises, suggestive of obstructive sleep apnea.

**Results**

The mean follow up period from the time of the sleep study was 4.6 (SD 2.85) years. The mean pain rate was 2.94 (SD 3.8) days per year; 9 of the 95 patients had no pain episodes recorded. There were 2 sickle-related deaths and 6 patients had a stroke. Chest syndrome was recorded in 12 patients, with a range of episodes per individual of 0 to 8 events. Table 1 shows the baseline characteristics and univariate analysis of the relationship between the risk factors and the average number of pain days per year in the study cohort. Lower baseline Hct and Hb were significantly associated with
increased pain rate, as was HbSS genotype. There were significant associations between a decreased pain rate and higher mean SaO2 (average fall 0.75 (0.58, 0.92) per unit increase in SaO2), higher minimum SaO2 and decreased percentage of sleep study with SaO2 <80% or <90%. There were no significant associations with the other variables. Multiple linear regression was used to quantify the association between overnight SaO2 measurements and pain, both before and after adjustment for potential confounding variables. Of the 5 overnight measurements, mean saturation was most strongly associated with average pain. After accounting for variability in mean saturation, only minimum saturation remained of borderline significance (p=0.051) when modelling the variation in pain rates. After adjustment for genotype (SC, SS, S(thal), dactylitis before 1 year of age, baseline Hb, HbF, early Hb and WBC, mean saturation remained significantly associated with pain rate (p<0.00005). The presence of dips was additionally significant within this model (p=0.007). An increase of one unit in mean SaO2 was associated with an average fall of 0.83 (0.58, 1.07) in the number of days pain per year (p<0.00005). The presence of dips was associated with 2.97 (0.85, 5.10) more days pain on average per year. The results were similar when adjusted for hematocrit in the 79 patients for whom it was available.

For patients who underwent adenotonsillectomy (n=28; 30%), there was a decrease in the number of days in pain from the year before to the year after surgery (3.75 vs. 2.64, a difference of -1.11 (95% ci -2.68, 0.46) days/year), which did not reach statistical significance (p=0.16, paired t-test). 9/27 patients who underwent adenotonsillectomy had sleep study data collected post- as well as pre-operatively because of persistent symptoms, at a median time post-operatively of 4.5 (range 0.5-7) years. Six still had significant dips in SaO2 as defined above and mean saturation fell
from an average of 94.8% to 92.9% (difference -1.9% (95% ci -5.9 to 2.0%), p= 0.29).

Interestingly, if the results are split into patients undergoing adenotonsillectomy for OSA (n=11) or for repeated infections (n=17), the OSA patients do not show any correlation with frequency of painful episodes but there was an association for those where the indication was recurrent infection (p= 0.02).

**Discussion**

In our study, low nocturnal oxygen saturation appears to be highly significantly associated with frequent painful vaso-occlusive crisis in SCD, perhaps because it is one of the factors involved in precipitating hypoxic-ischemic pathology in bone marrow. Interestingly, lower hemoglobin was associated with more frequent painful crises in these children, in contrast to the previous literature, but in line with our finding that low oxygen saturation is associated with anemia. It is possible that the paradoxical association of higher hemoglobin/hematocrit and oxygen saturation seen in adults with frequent painful crisis is not manifest in early childhood, perhaps because it depends on the degree of adaptive acclimatisation to chronic hypoxemia; future longitudinal studies may elucidate this. Increased viscosity as measured by haematocrit was significantly associated with an increased pain rate.

Our data require confirmation in other populations, as there are sources of bias. This is a hospital-based, rather than a birth cohort which may explain the high proportion of children with at least one painful episode requiring hospital attendance. We did not attempt to measure the experience of pain at home, which has considerable methodological difficulties. At the time of the study, most families in the local community used Queen Elizabeth Hospital for primary care, but with changes in the configuration of health services, children are now more likely to be managed at home.
and there are now validated methods of assessing pain outside hospital. We did not have the resources to undertake rigorous reproducibility testing of our home sleep studies. Since the mean saturation is a better predictor of frequent pain than frequent dips, it may be possible to screen the population using a short period of daytime pulse oximetry and we are at present investigating the reproducibility of clinic measurements and the correlation with overnight saturation monitoring.

Although UAO is relatively common in the sickle population it may not be the major cause of nocturnal hypoxemia, and in this study adenotonsillectomy did not significantly reduce the number of painful crises. Indeed, the main effect of adenotonsillectomy was seen in patients where the indication for operation was recurrent tonsillitis, suggesting that it is the absence of infection that may be the benefit and that this is the real risk factor in this group. Hypoxemia may persist round the clock, perhaps secondary to mechanisms other than UAO and chronic anemia. The size of the airway may be determined in early life, perhaps explaining why adenotonsillectomy does not always improve the oxygen saturation. Nocturnal hypoxemia might precipitate vaso-occlusion in the lung as well as the bone marrow, with progressive parenchymal lung injury and poor gas exchange; the investigation of this type of vicious cycle would require a longitudinal study with repeated lung function testing. However, it has long been postulated that hypoxia is a physiological precipitating factor in the formation of the sickled cell and it is the basis for avoidance of hypoxic environments, for example in anaesthesia and high altitude travel. The possibility that appropriate management of chronic hypoxemia reduces the incidence of stroke, acute painful crises, and death in children with SCD will be examined in the planned controlled trial, funded by the Stroke Association, of overnight oxygen supplementation.
### Table 1: Linear regression analysis of clinical, laboratory and sleep study variables against pain rate (number pain days/year of follow up)

<table>
<thead>
<tr>
<th>Risk Factors for Painful crises</th>
<th>Baseline Characteristics</th>
<th>Mean Pain Rate (SD)</th>
<th>Coefficient</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at sleep study (years)</td>
<td>95 8.2 2.1 -16.9</td>
<td>2.95 (3.78)</td>
<td>0.07</td>
<td>(-0.13, 0.28)</td>
<td>0.46</td>
</tr>
<tr>
<td>Gender: Male</td>
<td>54 (57%)</td>
<td>2.93 (3.85)</td>
<td>0.02</td>
<td>(-1.6, 1.6)</td>
<td>0.98</td>
</tr>
<tr>
<td>cf Female</td>
<td>41 (43%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickle Type: SS</td>
<td>74 (78%)</td>
<td>3.54 (4.08)</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>cf SC</td>
<td>14 (15%)</td>
<td>0.79 (0.74)</td>
<td>2.75</td>
<td>(0.6, 4.9)</td>
<td></td>
</tr>
<tr>
<td>Sβthal (cf SC)</td>
<td>7 (7%)</td>
<td>0.89 (1.08)</td>
<td>0.1</td>
<td>(-3.2, 3.5)</td>
<td>0.95</td>
</tr>
<tr>
<td>Dactylitis &lt; 1yr: YES</td>
<td>23 (24%)</td>
<td>4.44 (2.94)</td>
<td>1.6</td>
<td>(-0.4, 3.6)</td>
<td>0.11</td>
</tr>
<tr>
<td>NO</td>
<td>72 (76%)</td>
<td>2.85 (4.35)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Hb (g/dl)</td>
<td>95 8.8 6.3-13.3</td>
<td></td>
<td>-0.6</td>
<td>(-1.0, -0.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Baseline Hct</td>
<td>79 0.28 0.20-0.42</td>
<td></td>
<td>-23.72</td>
<td>(-37.8, -9.64)</td>
<td>0.0012</td>
</tr>
<tr>
<td>Mean Hb at 11-25m (g/dl)</td>
<td>95 9.1 6.0-12.1</td>
<td></td>
<td>-0.5</td>
<td>(-1.2, 0.2)</td>
<td>0.14</td>
</tr>
<tr>
<td>Mean WBC at 11-25m (10^9/L)</td>
<td>95 12.1 0.4-25.0</td>
<td></td>
<td>0.1</td>
<td>(-0.6, 0.3)</td>
<td>0.19</td>
</tr>
<tr>
<td>Baseline HbF (%)</td>
<td>95 6.9 0.2-21.8</td>
<td></td>
<td>-0.09</td>
<td>(-0.3, 0.09)</td>
<td>0.32</td>
</tr>
<tr>
<td>Mean nocturnal oxygen saturation</td>
<td>95 95.1 85.0-99.7</td>
<td></td>
<td>-0.8</td>
<td>(-0.6, -0.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% sleep study &lt;80%</td>
<td>95 0.6 0.25-5.0</td>
<td></td>
<td>0.7</td>
<td>(0.5, 0.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% sleep study &lt;90%</td>
<td>95 11.1 0.99-6</td>
<td></td>
<td>0.09</td>
<td>(0.06, 0.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Minimum SaO2 (%)</td>
<td>95 81.2 41-97.0</td>
<td></td>
<td>-0.1</td>
<td>(-0.2, -0.04)</td>
<td>0.004</td>
</tr>
<tr>
<td>Normal sleep study</td>
<td>64 (67%)</td>
<td>1.94 (2.77)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dips on sleep study</td>
<td>24 (25%)</td>
<td>8.24 (4.30)</td>
<td>1.4</td>
<td>(-0.01, 2.83)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

SS = homozygous sickle, SC = hemoglobin SC, Sβthal = Sickle-β-Thalassaemia, SD = standard deviation, m = months

Hb= hemoglobin, Hct= hematocrit, WBC= white blood cell count

*Average change in number of days pain/year between categories or, for continuous measurements, per unit increase in the risk factor.

*7 Cases with no dips but low baseline oxygen saturation excluded from the normal sleep study group.
References:


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