Sleep related upper airway obstruction and hypoxaemia in sickle cell disease

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Abstract
A cohort of 53 patients (age range 1–9;16–5 years) with sickle cell disease (49 homozygous SS and four Sβ-thalassaemia) was studied for evidence of sleep related upper airway obstruction (UAO). This involved (i) a clinical assessment based on a history of snoring, a score of tonsillar size, and (for 50 patients) over 21 nights of overnight multichannel respiratory recordings, and (ii) a blinded analysis of arterial oxygen saturation (SaO2) from the above recordings, and comparison with results from 50 healthy age matched controls of both white (n=25) and Afro-Caribbean race.

There was no difference in the baseline SaO2 values of the white and Afro-Caribbean controls. Eighteen patients with sickle cell disease (36%) were found to have sleep related UAO. The blinded analysis showed that eight patients (16%) had episodic hypoxaemia (SaO2 <80%, a value not observed in controls) and/or low baseline SaO2 values (<95–8%, the lowest value seen in the controls).

Postoperative assessment was undertaken in 15 patients who underwent adenotonsillectomy. All demonstrated an improvement in symptoms and a reduction or abolition of episodic hypoxaemia. Of the 47 patients assessed when free of UAO (not demonstrated on screening, n=32, or resolved following surgery, n=15), seven continued to show baseline hypoxaemia.

Sleep related UAO and baseline hypoxaemia are common complications of sickle cell disease in children.

Sickle cell disease has an appreciable morbidity and mortality, particularly in infancy and early childhood. There is still incomplete information, however, on the factors which increase the risk for complications of the disease, in particular the vaso-occlusive crises. The latter result from the sickling of red blood cells, after the polymerisation of deoxygenated sickle cell haemoglobin. Factors recognised as precipitating this process include dehydration, fever, acidosis, and hypoxaemia.

In recent years, there have been reports that vaso-occlusive pathology may result from undetected hypoxaemia, in some cases secondary to sleep related upper airway obstruction (UAO). These reports include descriptions of patients who have had repeated sickle cell crises and/or cerebrovascular accidents occurring in association with severe sleep related UAO. In an attempt to determine the true incidence of UAO, populations of patients with sickle cell disease have been screened for the presence of UAO, using either questionnaires or outpatient clinical assessment. These have revealed significant numbers of patients with a history compatible with sleep related UAO, but have not documented the prevalence of resultant hypoxaemia in patients with sickle cell disease.

To assess the prevalence of sleep related UAO and hypoxaemia, as well as its response to treatment, we studied prospectively a cohort of patients with sickle cell disease, utilising overnight sleep recordings in addition to clinical assessment. As the normal data for these studies were based on pulse oximetry values obtained in healthy children with light skin colour, we also compared recordings in black and white control children.

Subjects and methods
PROTOCOL FOR INVESTIGATION
The protocol included (i) documentation by a haematologist of signs and symptoms of UAO, (ii) overnight multichannel respiratory recordings and clinical assessment performed by a paediatric respiratory unit, (iii) examination and intervention by an ear, nose, and throat surgeon, followed by postoperative physiological recordings, and (iv) a blinded, case-controlled analysis of oxygenation from the overnight physiological recordings. Informed consent was given by all parents and, where appropriate, by the patients themselves. Ethical approval was obtained to study the controls.

SUBJECTS
The cohort under study included all patients (n=53) with homozygous sickle cell anæmia (SS) (n=49) and Sβ-thalassaemia (n=4) over 20 months of age who were attending the Central Middlesex Hospital paediatric haematology clinic. The lower age limit was chosen to include the period of normal lymphoid tissue growth, considered to be a contributory mechanism for UAO in patients with sickle cell anæmia. The patients were 18 boys and 35 girls, and ranged in age from 1–9;16–5 years (median 7;8).

One girl, aged 13 years, had undergone adenotonsillectomy before the study for symptoms of sleep related UAO. The remaining 52 patients had intact tonsils and adenoids. Three boys with SS had suffered cerebrovascular accidents, and an additional boy, also with SS, showed cerebral atrophy on computed tomography but without clinical signs. Another boy...
with SS, who was studied at the age of 4-1 years, died 1-1 years later from pneumococcal sepsicaemia.

**CONTROLS**

The controls (n=50) for the blinded analysis of oxygenation were matched to the subjects by age, resulting in median patient-control difference of 2 months (range 0 to 13). They came from two sources: (i) a random selection (n=25) from a group of healthy white children (n=45) who volunteered for previous studies. Their ages ranged from 1-9 to 16-3 years (median 6-9); there were 15 girls and 10 boys, and (ii) siblings (n=25) of patients with sickle cell disease who were themselves documented to be free of the disease; they were volunteers from families attending the haematology clinics at the Central Middlesex and Royal Berkshire Hospitals. Their ages ranged from 2-0 to 13-3 years (median 8-8); there were 14 girls and 11 boys.

**CLINICAL ASSESSMENT**

During haematology clinic visits, parents were asked about the presence of noisy breathing during sleep (snoring) and each tonsillar size was scored by visual examination from 0 (absent) to 6 (at the midline). UAO was considered possible in patients who snored regularly and whose combined tonsil size score was ≥8. These patients were referred to the paediatric respiratory unit for further assessment. All other patients without obstructive signs or symptoms were also asked if they would undergo specialist respiratory assessment in order to establish the sensitivity of an outpatient assessment in the detection of UAO. Three symptom-free patients refused respiratory assessment.

The 50 patients tested were 17 boys and 33 girls, with a median age of 8-0 years (range 1-9 to 16-5); 46 had SS disease and four Sp'. Their specialist assessment followed a clinical protocol used by our group to screen children for UAO.11-12 This included (i) ascertainment from the parents' history whether the child showed any of the following signs during sleep: inspiratory stridor (snoring), chest wall recession, sudden wakennings with a startle or gasp, restlessness, mouth breathing, and excessive sweating; (ii) physical examination both awake and asleep, and (iii) data from a overnight tape recording of respiratory variables (see below). The latter was analysed for evidence of increased inspiratory resistance on the chest wall movement waveforms, and levels of arterial oxygen saturation (Sao2) and end tidal carbon dioxide. The diagnosis of UAO was confirmed if there were characteristic clinical symptoms and signs, in combination with an abnormal recording, and referral was made for an ear, nose, and throat assessment. The effect of any consequent surgical intervention was checked by repeating the specialist respiratory assessment.

The 12 hour overnight tape recording performed on each subject and control comprised the following signals: (i) Sao2 from a pulse oximeter (Nellcor N-200) modified to provide beat-to-beat measurements; (ii) the photoplethysmographic pulse waveforms from which Sao2 was derived; these were used to identify and exclude Sao2 measurements associated with movement artefact; (iii) chest wall movements from respiratory inductance plethysmography (Studley Data Systems) using a purpose made vest over the chest wall (PK Morgan) and from an abdominal volume expansion capsule (Graseby Dynamics), and (iv) end tidal carbon dioxide, sampling from just below one nostril via a catheter leading to an infrared analyser (Engstrom Eliza). This last signal was measured in all patients but a minority of controls. The recording technique has been described in detail elsewhere.11 The majority of recordings on patients was performed in hospital (82%). The remainder were carried out in the children's homes, as were those on all of the control children. The recorded signals were printed out, using an ink jet chart recorder (Siemens 34T), at 3-2 mm/second.

**CASE-CONTROL STUDY OF OXYGEN SATURATION**

On completion of the clinical part of the study, a blinded assessment of Sao2 was carried out on the overnight recordings of patients and controls. This was performed by two workers without knowledge of the source of the data and working to a protocol established for earlier studies.13-14 Breathing pattern was classified as being either regular or non-regular; regular breathing pattern was signified by periods lasting at least one minute in which breathing movements were steady in rate and amplitude; all other periods were classified as non-regular.13-14 Artefact on the Sao2 signal was excluded by examination of the pulse waveforms. The tracings were then examined for:

(i) **Baseline Sao2 values**. These were measured at the end inspiratory peak of five successive breaths in the centre of each period of regular pattern breathing at least 10 seconds from disturbance of the chest wall movement by high or apnoeic pause. The mean of these measurements was calculated.

(ii) **Episodes of hypoxaemia despite continued breathing movements**. These were defined as episodes in which Sao2 fell to ≤80%; the duration of each was totalled and the frequency per hour of artefact free recording was calculated. Apnoeic pauses were identified where there was a cessation of chest wall movement with a duration of ≥4 seconds, and episodes of desaturation were discounted if they showed a temporal relationship with such pauses; that is where the beginnings of a pause in breathing and of a subsequent desaturation were separated by 2 to 12 seconds. This excluded the episodic hypoxaemia that has been demonstrated frequently and normally to follow apnoea pauses in healthy infants14 and young children, studied under a protocol identical to that used here.

The values of baseline Sao2 and episodic hypoxaemia were compared (i) between controls of different race, (ii) between patients and controls, and (iii) in patients before and after adenotonsillectomy. The significance of these differences in Sao2 were tested by Wilcoxon
signed rank, Wilcoxon rank sum, or Fisher's exact tests. As evidence was already available to suggest an increased frequency of UAO in sickle cell disease one tailed tests were used for the case-control comparisons. A two tailed test was used for the comparison of oxygenation in the control groups of different race.

**Results**

**CLINICAL ASSESSMENT**

Twenty nine (55%) of the 53 patients were identified from the outpatient history and clinical examination as having symptoms and signs suggestive of sleep related UAO.

Eighteen (36%) of the 50 patients who underwent specialist respiratory assessment were confirmed as having UAO. Their ages ranged from 2·3–16·5 years (median 6·3). Fourteen of the 18 (78%) had been among the 29 identified at the haematology clinic; the remaining four were from the 24 patients considered from history and examination not to have UAO (8% of all patients).

Patients with documented UAO included one patient with Sjögren disease, and also two of the three who had suffered cerebrovascular accidents and the subject with cerebral atrophy. The subject who subsequently died did not demonstrate UAO at the time of the recording.

In the opinion of the ear, nose, and throat surgeons, 17/18 patients with documented UAO needed adenotonsillectomy (one patient refused an ear, nose, and throat referral); 16 have now undergone surgery (one patient refused this). Postoperative respiratory assessment was undertaken in 15 patients (one was lost to follow up); all were considered to have an improvement in clinical symptoms and signs, suggestive of complete or substantial resolution of their UAO.

**CASE-CONTROL STUDY**

**Abnormal hypoxaemia**

In eight of 50 patients, abnormal hypoxaemia was detected on recordings: all eight had baseline hypoxaemia and four also demonstrated episodic hypoxaemia. These latter four patients were also among those with the five lowest baseline values.

**Baseline SaO²**

Within the control group, the median baseline SaO² in Afro-Caribbean children was 99·2% (range 95·8–100) and in white children 99·5% (range 96·2–100; p>0·05 Wilcoxon rank sum).

Baseline saturation was significantly lower in the patients (p<0·05, Wilcoxon signed rank). The median value in the patients was 99·0% (range 88·6–100) and in the controls the median was 99·3% (range 95·8–100). Eight patients (16%) had values below the control range.

The four patients with Sjögren disease demonstrated baseline values >99·9%.

**Episodic hypoxaemia ≤80%**

Two of the 50 patients had poor quality SaO² signals through the majority of non-regular pattern breathing. Their recordings could not therefore be included in an analysis of episodic hypoxaemia (SaO² measurements during regular breathing were satisfactory). None of the controls, but 4/48 (8%) patients, demonstrated episodes in which SaO² fell to ≤80% (p>0·05, Fisher's exact test). In these four patients the number of episodes/hour was 0·2, 0·5, 16·4, and 80·7 respectively, and these produced a totalled duration of hypoxaemia of 1·9, 2·4, 89·1, and 514·1 seconds/hour. All of these four patients had baseline SaO² below the range in the controls.

**Oxygen saturation and UAO**

Thirteen patients had UAO but no evidence of hypoxaemia. The remaining five patients with UAO had abnormal hypoxaemia: four with episodic hypoxaemia plus an abnormally low baseline (88·6, 91·1, 92·1, and 93·5%), and one patient with an abnormally low baseline value alone (92·2%). Three patients thus had abnormally low baseline SaO² without evidence of UAO (93·6, 94·1, and 95·6%). The patients with UAO had significantly lower baseline than their controls (p<0·05, Wilcoxon signed rank) while the difference for the 32 patients without UAO was non-significant (p>0·05, Wilcoxon signed rank).

In the 15 patients who were retested after adenotonsillectomy, baseline SaO² before surgery was 88·6–100% (median 98·5%) and after surgery 90·0–100% (median 99·4%; p>0·05 Wilcoxon signed rank). Before surgery five patients had values for baseline SaO² which fell below the control range; four had low values after surgery (90·0, 91·6, 94·6, and 95·0%). All four of the patients with episodic hypoxaemia ≤80% were reassessed after surgery; in two this abnormality was not identified, and in two it continued but at reduced levels (durations falling from 89·1 to 14·2, and 1·9 to 1·7 seconds/hour respectively).

Of the 47 patients tested when free of UAO, that is the group in which it was not demonstrated on screening (n=32) or the group in which it was shown to have resolved after surgery (n=15), seven patients (15%) continued to demonstrate baseline SaO₂ values (90·0–95·6%) below the control range.

**Discussion**

Based on a history and outpatient clinical examination, 29/53 (55%) of our patients with sickle cell anaemia and Sjögren disease were considered to have symptoms and signs compatible with sleep related UAO. This agrees with the data of Wittig et al who, from questionnaires, found 28/65 (43%) of patients with SS disease to snore when compared with 18/102 (18%) of controls (siblings without SS). Maddern et al found 21 out of approximately 400 (5%) children and adolescents with SS disease to have UAO. This was based on clinical assessment and confirmed by subsequent polysomnography (including measurement of oxygenation).9 Recordings were not performed, however, on
the asymptomatic patients in this cohort. Snoring and large tonsils are common, and their presence does not predict those who will have abnormal hypoxaemia.15

The detection of abnormalities in oxygenation is best performed by an assessment involving long term non-invasive recordings of oxygen saturation and breathing patterns. The pulse oximeters used in such studies must first have been validated against arterial line measurements. Recordings of the light plethysmograph waveforms from the pulse oximeter are required in order to identify any falls in SaO2 which are artefactual (usually due to body movements). Printouts from the oximeter which do not provide this latter signal do not allow reliable quantification of baseline hypoxaemia and the amount of episodic hypoxaemia.

Pulse oximetry has been reported to be accurate in infants and children who have sickle cell disease16 and black skin.17 Our study supports the latter observation by showing that healthy children with black skin have baseline SaO2 values equivalent to those of children with light skin. Pulse oximetry is reliable in SS disease because oxygenated and deoxygenated haemoglobin S have absorbances at wavelengths of light that are similar to those of haemoglobin A.16 The oxygen dissociation curve in patients with SS disease is, however, shifted to the right, so that small falls in arterial oxygen tension may produce large changes in SaO2.16 It is the latter which more directly relates to the process of intracellular sickling. Pulse oximetry was therefore considered a reliable measure of clinically relevant oxygenation in this study.

In our cohort of patients with SS and Sp6 disease, 18/50 (36%) were found to have UAO documented on their overnight recording. This included 14 of the 29 considered clinically to have UAO, giving a positive predictive value of 48% and sensitivity of 78% for the 'clinical detection' of abnormalities at recording. It would be wrong to assume, however, that a history of snoring, large tonsils, and a normal recording mean that symptoms of UAO without blood gas abnormality are unimportant. All our patients were free of respiratory symptoms at the time of their recordings. It is possible that during respiratory infections affecting, for example, upper airway patency, physiological abnormalities such as hypoxaemia may have developed and contributed, along with fever, dehydration and acidosis, to vaso-occlusive pathology. Airway and alveolar hypoxia during infection may exacerbate intrapulmonary shunting and produce acute deteriorations in oxygenation,18 one possible mechanism for sudden and unexpected death in young children with SS disease.19

We did not prospectively collect information on vaso-occlusive episodes in our patients and relate it to the results of our physiological recordings. We cannot, therefore, confirm or refute the possibility that sickle crises are temporally associated with hypoxaemia accompanying UAO. To do this would require prospective oxygen measurements on a population of patients with sickle cell anemia.

An examination of physiological recordings during sleep requires a knowledge of what is normal and for this reason we have collected our own control data. The recordings performed for the specialised clinical assessment were not blinded and were taken in conjunction with the history. It is possible that bias could have occurred in the interpretation of the results. We do not know that of the 18/50 (36%) with UAO patients, some patients have a persistently low baseline SaO2 level which remains unexplained.

Previous studies have reported that the hypoxaemia developing during sleep in SS disease is due to hypoventilation.5 Sleep related UAO will produce alveolar hypoventilation, the usual finding on sleep recordings being that of intermittent episodic hypoxaemia. Although baseline hypoxaemia may occur with prolonged and severe UAO, its continued presence after adenotonsillectomy in some of our patients, and its presence in three patients without UAO, suggests that chronic lung or pulmonary vascular disease may have been responsible. Wall et al have previously documented arterial hypoxaemia and increased calculated shunt, despite normal lung mechanics, in children with SS disease.20 This too could represent a chronic lung disease with ventilation-perfusion mismatch similar to that found in adults with sickle cell disease.21

One potentially treatable cause of hypoxaemia in our patients was sleep related UAO due to enlarged tonsils and adenoids, an increasingly recognised reason for adenotonsillectomy in otherwise healthy children. Although our assessment of tonsil size was not case-controlled, adenotonsillar hypertrophy may be more common in sickle cell disease. Possible explanations have included lymphoreticular hypertrophy as a result of the splenic atrophy consequent on repeated sickling in the splenic sinuses, repeated infections or increased haemopoietic needs.9 Evidence for the last, however, has not been borne out by examination of removed tonsils.9 It is also possible that changes in the anatomy of the upper airway, perhaps the result of the bone marrow effects of SS disease, may produce a relative narrowing, making the child susceptible to 'normal' adenotonsillar tissue. Such anatomical abnormalities have been suggested as a mechanism for UAO.15 Surgery to remove the tonsils and adenoids in patients with sickle cell disease has greater risks than that in otherwise healthy children, particularly in a third world setting. However, with adequate attention to hydration, temperature and oxygen monitoring, the outcome in our patients has been good. Only one of our patients underwent exchange transfusion after operation, because he had cardiac failure. This procedure is performed routinely by others.9

In summary, abnormal oxygenation was a common finding in a cohort of children with sickle cell disease. Where there is a history of possible sleep related UAO, or of frequent vaso-occlusive crises, such patients should undergo...
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physiological studies during sleep to determine whether UAO and/or abnormal oxygenation is present. If UAO with episodic hypoxaemia is present, adenotonsillectomy may correct this. However a proportion of the hypoxaemia present in children with SS disease is unrelated to UAO. Further studies are required to ascertain whether baseline or episodic hypoxaemia and vaso-occlusive pathology are temporally related, thus leading to strategies that may prevent some of the morbidity and mortality associated with sickle cell disease.

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