SLEEP DISORDERED BREATHING

Is there a familial association between obstructive sleep apnoea/hypopnoea and the sudden infant death syndrome?


Background: One postulated cause of the sudden infant death syndrome (SIDS) is upper airway obstruction during sleep. Several studies have suggested that SIDS may be more common in families with obstructive sleep apnoea/hypopnoea syndrome (OSAHS), but were limited by uncertainty as to whether the deaths were due to SIDS. We have tested the hypothesis that parents of true SIDS cases have an increased frequency of apnoeas and hypopnoeas during sleep.

Methods: The parents of 269 rigorously determined SIDS cases were invited for single night polysomnography and daytime ventilatory control measurement.

Results: Parents of 198 cases were identified but 152 did not respond or declined. Fifty five parents of 34 cases were studied and matched for age, height, and weight to 55 subjects from general practice registers. There was no difference in breathing during sleep between the parents of SIDS cases (median (IQR) 3.9 (3.2, 10.7) apnoeas/hypopnoeas/h) and controls (6.7 (4.0, 12.2) apnoeas/hypopnoeas/h; p = 0.47), but the SIDS parents had lower minimum nocturnal oxygen saturation (median (IQR) 92 (89, 93)%) than controls (92 (90, 94%); p = 0.048). There were no major differences in control of breathing when awake between SIDS parents and controls.

Conclusions: These results provide no evidence to support an association between SIDS and OSAHS. However, the minor impairment of oxygenation during sleep in SIDS parents requires further study.

The sudden infant death syndrome (SIDS) is a condition of unknown aetiology and is the most common cause of death in babies under the age of 1 year. There have been many theories about the cause of SIDS, including disorders of cardiac, respiratory and thermal control, but most are based on anecdote or association and none have been proved to cause many of these tragic deaths.

One theory is that SIDS may be caused by obstructive apnoeas in infants who die because they fail to arouse. There is some evidence in favour of this hypothesis including:

- a small increase in obstructive apnoeas in infants who subsequently die of SIDS;
- upper airway narrowing in SIDS cases and in cases of "near miss SIDS";
- similar facial characteristics in SIDS cases and in non-obese patients with sleep apnoea/hypopnoea syndrome (OSAHS), with back setting of the maxilla;
- the subsequent development of obstructive sleep apnoea in cases of "near miss SIDS";
- an increased frequency of reported SIDS in family members of patients with OSAHS.

However, these data are suggestive rather than conclusive. The studies suggesting an increased frequency of SIDS in the family members of patients with OSAHS may be affected by recall bias, with OSAHS patients being more likely than normal subjects to have asked relatives about unexplained deaths during sleep. In addition, these studies are retrospective and the possibilities of other causes of death in SIDS cases cannot be excluded, despite attempts to do so.

We therefore tested the hypothesis that, if SIDS is caused by obstructive sleep apnoea (OSA) in children and is familial related to OSAHS, then the parents of true SIDS cases would have an increased frequency of apnoeas and hypopnoeas during sleep.

METHODS

Sleep histories and overnight polysomnography were obtained for parents of SIDS cases and age, sex, height and weight matched controls. The study was approved by the local medical ethical advisory committees and all subjects gave written informed consent.

Case selection

SIDS cases were identified by the specialist pathologist in SIDS in the departments of paediatric pathology at the Royal Hospital for Sick Children, Edinburgh and Yorkhill Hospital, Glasgow during the period 1987–98. In all SIDS cases known causes of sudden infant death which are identifiable after death had been excluded by expert medical examination and the Procurator Fiscal led confidential enquiries including detailed post mortem examination with cultures, pathological evaluation, neuropathology, appropriate electromicroscopy, enzyme, toxicological investigations, and whole body radiology. The parents of 269 consecutive SIDS cases were invited to participate (fig 1), all approaches being made through the family practitioner of the SIDS victim at the time of death. The parents of 57 of the SIDS cases could not be traced by the family practitioner and the family practitioners indicated that the parents of 14 cases should not be contacted for emotional reasons. The parent(s) of the remaining 198 cases were still registered with their family practitioner.

Abbreviations: AHI, apnoea/hypopnoea index; fR, respiratory frequency; OSA, obstructive sleep apnoea; OSAHS, obstructive sleep apnoea/hypopnoea syndrome; SaO2, oxygen saturation; SIDS, sudden infant death syndrome; TE, expiratory time; TI, inspiratory time; VE, minute volume; VT, tidal volume.
but 125 parent pairs did not respond to our two letters of
invitation, 25 parent pairs were identified by the postal
service as having moved away, the parents of two cases
decided to participate, and 12 pairs agreed to take part but
did not attend for their sleep studies. Fifty five parents of 34
SIDS cases therefore participated in the study.

Controls were obtained from family practice registers and
matched with the parents studied on a one to one basis for
sex, age within 5 years, height to within 5 cm, and weight to
within 5 kg. Each was approached by an independent
research guardian and asked to participate in an unspecified
medical research study. One hundred and thirty three
possible subjects were approached before 55 suitable controls
agreed.

Protocol
All SIDS parents and control subjects and their partners
underwent overnight polysomnography using Compumedics S
system (Compumedics, Australia) and our normal techni-
cues. All had their height and weight measured. SIDS
system (Compumedics, Australia) and our normal techni-
ques. All had their height and weight measured. SIDS
parents and controls were invited to have lateral cephalo-
metry to determine upper airway dimensions and facial bone
structure.

The subjects were asked to return for a further half day
when the ventilatory responses to hypoxia and hypercapnia
were measured by dynamic end tidal forcing using our
standard techniques. Isocapnic hypoxia (saturation 85%) was
maintained for 7 minutes. The isoxic hypercapnic
response was expressed as the VE/saturation (VE/SpO2: l/min/%) relationship and the hypercapnic response was expressed as the VE/PeCO2 (l/min/kPa) relationship and intercept B (kPa).14

Analysis of data
Data were analysed using the two tailed paired t test or
Wilcoxon rank sign test with Bonferroni correction for multi-
ple comparisons, as appropriate. Results are expressed as mean
(SD) or median and interquartile range (IQR), as appropriate.

RESULTS
Sleep studies
Fifty five SIDS parents and 55 control subjects had overnight
polysomnography. There were no significant differences
between the parents and controls for age (37 (6) years v 37
(6) years; p = 0.26), sex (parents 26M, controls 26M), height
(1.69 (0.09) m v 1.69 (0.08) m; p = 0.15), or weight (75.9
(16.8) kg v 76.8 (16.2) kg; p = 0.19).

There was no significant difference in the apnoea/
hypopnoea index (AHI) between parents and controls (median 5.9 (IQR 3.2, 10.7) apnoeas+hypopnoeas/h slept
for SIDS parents v 6.7 (4, 12.2) apnoeas+hypopnoeas/h slept
for controls; p = 0.48; table 1). SIDS parents had statistically
significantly lower minimum nocturnal oxygenation (median
92% (IQR 89, 93) for parents v 92% (90, 94) for controls;
p = 0.048). There was a trend towards more episodes of 4%
O2 desaturation during sleep in the SIDS parents (p = 0.068).
There was no difference between the groups in the time with
oxygen saturation below 90%, in awake oxygen saturation,
or in arousals from sleep.

Cephalometry
Cephalometry was performed in 44 of the 55 matched pairs;
at least one member of the other 11 pairs declined the
radiographic exposure. There was no significant difference in
any skeletal length or angle between the two groups (table 2,
fig 2), nor was there any evidence of cephalometric
predisposition to upper airway narrowing in either sex of
SIDS parents when comparisons were performed within the
sex.

Ventilatory responses
Nine pairs of subjects successfully completed ventilatory
response testing. There were no significant differences in
baseline end tidal gas tensions or ventilatory pattern at any
time during the study between the two groups when
breathing air, nor in hypoxic or hypercapnic responses
(hypoxic response: median (IQR) −0.19 (−0.41, −0.10) l/
in% in parents, −0.13 (−0.67, −0.08) l/min% in controls,
p = 0.9; hypercapnic response: median (IQR) VE/PeCO2 7.69
(5.88, 19.70) l/min/kPa in parents, 7.70 (4.65, 15.1) l/min/
kPa in controls, p = 0.3; intercept B: median (IQR) 4.06 (3.75,
4.57) kPa in parents of SIDS cases, 4.34 (3.65, 4.81) kPa in
controls, p = 0.9). Following addition of the resistive load
there was a significant reduction in inspiratory time (T i),
expiratory time (T e), and respiratory frequency (FR) and an
increase in tidal volume (Vt) in both groups (table 3). There
were significant differences between the controls and the
patients in the resistive loading induced changes in T i, T e,
and minute volume (VE) (table 3).

DISCUSSION
This study found no difference in the breathing pattern
during sleep between parents of SIDS cases and control
subjects. This finding is contrary to our original hypothesis

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Figure 1 Subject recruitment to the study.
and thus does not provide any evidence of a familial association between abnormal breathing during sleep in adults and SIDS in their children. Some of the previous evidence in favour of a possible association is circumstantial and possibly influenced by recall bias and uncertainty about the accuracy of the diagnosis of SIDS. The current study avoids these problems by being based on thoroughly investigated index cases of SIDS and on objective measurements of breathing during sleep. It also included scrupulous matching of the parents with community controls. Recent studies have given conflicting results with no evidence of a familial relationship between OSAHS and SIDS in an Icelandic population study.15 An Australian study showed a much higher rate of OSAHS (19 out of 20) in infants from families where there were multiple histories of SIDS, or OSA.16 However, they found a much lower frequency of OSAHS (31 of 105) in infants in whose family there had been only one case of SIDS or an apparent life threatening event.17

It is possible that the greater hypoxaemia permitted during sleep in the parents of SIDS cases reflects a decreased arousability to hypoxic events. However, that was not the a priori hypothesis of this study and independent confirmation is required.

Despite previously reporting that babies who died of SIDS had back set maxillae and mandibles,6 we did not find any difference in the facial structure between parents of SIDS cases and population controls. The sample sizes in this study (44 matched pairs for cephalometry) were much larger than in previous studies and ascertainment of the SIDS cases was much better than in the previous study in OSAHS families where SIDS was based on family members’ reports without inquiry or necroscopic confirmation. It therefore seems unlikely that there is any familial facial structure abnormality which predisposes to SIDS.

However, this study has significant limitations, including recruitment rates and power. Only 55 of a potential total of 542 SIDS parents were studied. Many of those not studied (n = 198) could not be traced or were considered by their parents studied were different from those who did not participate. This rate reflects a combination of the emotional sensitivity of the subject to many parents, the high number of young single parent families, the high number with social problems with resulting difficulties in participating, and the frequency with which young often single parents change addresses. We made very strenuous efforts within the limits of the sensitivity of the problem to maximise recruitment. We believe that the recruitment rate we obtained, while disappointing, was as high as could be ethically obtained among SIDS parents. We have no reason to believe the parents studied were different from those who did not participate, but have inadequate demographic information about these individuals (because of the sensitivity of the topic) to analyse this. The power of the study was adequate to determine significant differences in breathing during sleep or facial structure, but the number of subjects agreeing to participate in the ventilatory control studies limited the power of these observations as discussed below.

Another limitation is the number of statistical comparisons made (n = 35). This in no way detracts from the certainty of the negative observation on our a priori hypothesis that parents of SIDS cases would have more apnoeas and hypopnoeas than controls. It does, however, cast some doubt on the certainty of the six “statistically significant” differences observed as, by chance alone, two of the comparisons

Table 1 Results of sleep studies in parents of SIDS cases and controls

<table>
<thead>
<tr>
<th></th>
<th>SIDS parents (n = 55)</th>
<th>Controls (n = 55)</th>
<th>p value</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time (min)</td>
<td>396 (363, 416)</td>
<td>393 (335, 417)</td>
<td>0.39</td>
<td>–1 (-20, 43.5)</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>84.3 (79.4, 88)</td>
<td>83.7 (74.2, 87.9)</td>
<td>0.42</td>
<td>1.9 (-4.4, 6.1)</td>
</tr>
<tr>
<td>AHI (/h slept)</td>
<td>5.9 (3.2, 10.7)</td>
<td>6.7 (4, 12.2)</td>
<td>0.48</td>
<td>0.01 (-4.2, 2.2)</td>
</tr>
<tr>
<td>Arousals (/h slept)</td>
<td>18.5 (15.8, 25.1)</td>
<td>17.1 (13.2, 24.6)</td>
<td>0.36</td>
<td>1.1 (-5.9, 6.8)</td>
</tr>
<tr>
<td>Awake SaO2 (%)</td>
<td>97.6 (96.1, 98.2)</td>
<td>97.6 (96.5, 98.4)</td>
<td>0.58</td>
<td>0.04 (-1.5, 1.5)</td>
</tr>
<tr>
<td>Minimum SaO2 (%)</td>
<td>92 (89, 93)</td>
<td>92 (90, 94)</td>
<td>0.048</td>
<td>1 (-4, 2)</td>
</tr>
<tr>
<td>4% dips/h</td>
<td>0.9 (0.3, 2.9)</td>
<td>0.6 (0, 1.9)</td>
<td>0.068</td>
<td>0.3 (-0.9, 1.7)</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range).

Figure 2 Diagrammatic representation of cephalometry measurements. Go = gonion; Gn = gnathion; Ar = articulare; ANS = anterior nasal spine; PNS = posterior nasal spine; Ba = basion; H = hyoid; MP = mandibular plane; PhW = pharyngeal wall; S = sella; N = nasion; A = subspinale; B = supramentale.
One of our SIDS parents had more than 15 apnoeas + pnoeas/h slept. Lower drives in the SIDS parents reported in other studies. However, we observed no trend towards the substantially statistical error as we were only able to obtain measurements studied only nine pairs of subjects in this component of the study and individuals vary in how they adapt to resistive loading. The results suggest possible differences in non-chemical ventilatory control in families of SIDS cases and merit further investigation.

Table 2  Mean (SD) cephalometric measurements in parents of SIDS cases and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>SIDS parents (n = 44)</th>
<th>Controls (n = 44)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Go–Gn (mm)</td>
<td>82 (7)</td>
<td>83 (5)</td>
<td>0.74</td>
</tr>
<tr>
<td>Go–Ar (mm)</td>
<td>55 (6)</td>
<td>54 (7)</td>
<td>0.21</td>
</tr>
<tr>
<td>ANS–PNS (mm)</td>
<td>57 (4)</td>
<td>55 (5)</td>
<td>0.17</td>
</tr>
<tr>
<td>PNS–Ba (mm)</td>
<td>47 (7)</td>
<td>48 (5)</td>
<td>0.33</td>
</tr>
<tr>
<td>HMP (mm)</td>
<td>20 (6)</td>
<td>18 (18)</td>
<td>0.42</td>
</tr>
<tr>
<td>PNS–PhW (mm)</td>
<td>28 (5)</td>
<td>26 (6)</td>
<td>0.09</td>
</tr>
<tr>
<td>SNA (°)</td>
<td>82 (4)</td>
<td>83 (5)</td>
<td>0.23</td>
</tr>
<tr>
<td>SNB (°)</td>
<td>78 (4)</td>
<td>79 (4)</td>
<td>0.48</td>
</tr>
<tr>
<td>NSba (°)</td>
<td>127 (6)</td>
<td>128 (5)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Go = gonion; Gn = gnathion; Ar = articulare; ANS = anterior nasal spine; PNS = posterior nasal spine; Ba = basion; H = hyoid; MP = mandibular plane; PhW = pharyngeal wall; S = sella; N = nasion; A = subspinale; B = supramentale.

Table 3  Effect of resistive loading

<table>
<thead>
<tr>
<th>Variable</th>
<th>SIDS parents (n = 9)</th>
<th>Controls (n = 9)</th>
<th>Change from baseline to resistance (parents – controls)</th>
<th>p value for differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ti (s)</td>
<td>1.26 (1.21, 1.71)</td>
<td>1.65 (1.32, 2.04)</td>
<td>-0.87 (-1.75, -0.14)</td>
<td>0.021</td>
</tr>
<tr>
<td>Tr (s)</td>
<td>2.16 (1.70, 2.48)</td>
<td>2.69 (2.23, 3.37)</td>
<td>-0.13 (-2.15, -0.46)</td>
<td>0.015</td>
</tr>
<tr>
<td>fR (breaths/min)</td>
<td>17.9 (15.0, 21.0)</td>
<td>14.4 (11.0, 17.6)</td>
<td>-0.4 (-2.7, -4.5)</td>
<td>0.374</td>
</tr>
<tr>
<td>VT (l)</td>
<td>0.64 (0.47, 0.67)</td>
<td>0.68 (0.57, 0.92)</td>
<td>0.05 (0.74, 1.30)</td>
<td>0.953</td>
</tr>
<tr>
<td>Ve (l/min)</td>
<td>10.00 (8.83, 11.05)</td>
<td>9.13 (8.90, 11.5)</td>
<td>0.12 (0.74, 1.30)</td>
<td>1.02</td>
</tr>
<tr>
<td>Vr/Ti (l/s)</td>
<td>23.4 (22.8, 29.7)</td>
<td>22.2 (21.4, 28.8)</td>
<td>0.02 (13.9, 19.6)</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Ti = inspiratory time; Tr = expiratory time; fR = respiratory frequency; VT = tidal volume; Ve = minute volume.

References

Adjuvant chemotherapy and survival in completely resected non-small cell lung cancer


The role of adjuvant chemotherapy in patients with completely resected non-small cell lung cancer (NSCLC) is unclear. In this randomised controlled trial, patients with pathologically documented NSCLC (stages I–III) were assigned to either cisplatin based chemotherapy or observation within 60 days of surgery. The primary outcome measure was overall survival.

A total of 1867 patients of median age 59 years from 148 centres in 33 countries were randomised to adjuvant chemotherapy (n = 932) or observation (n = 935). The median duration of follow up was 56 months. There was an absolute increase in 5 year survival of 4.1% in the adjuvant chemotherapy group compared with controls (44.5% vs 40.4%; hazard ratio for death 0.86; p < 0.03). Disease free survival rate at 5 years was also higher in the patients assigned chemotherapy (39.4% vs 34.4%; hazard ratio 0.83; p = 0.003). There were no significant interactions between treatment effect and the patients’ baseline characteristics or other treatment options on survival. Seven patients (0.8%) died from chemotherapy induced toxic effects and 23% of patients had life threatening adverse effects, mostly attributable to myelotoxicity.

This study suggests a role for cisplatin based adjuvant chemotherapy in patients with NSCLC and shows a survival benefit similar to that obtained with adjuvant chemotherapy for breast, colon, and ovarian cancer. However, other studies of adjuvant chemotherapy in this setting have failed to demonstrate a survival advantage. A meta-analysis of all adjuvant trials is currently underway.

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