Nasal and intrapulmonary haemorrhage in sudden infant death syndrome

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Abstract

Background—Fresh intrapulmonary and oronasal haemorrhages in cases of sudden infant death syndrome (SIDS) might be markers for accidental or intentional smothering inappropriately diagnosed as SIDS.

Aim—To compare the incidence, epidemiological association, and inter-relation of nasal haemorrhage, intrapulmonary haemorrhage, and intrathoracic petechiae in infant deaths certified as SIDS.

Methods—In SIDS cases from a large nationwide case-control study, a wide range of variables were compared in cases with and without reported nasal haemorrhage and, in a subgroup of cases, in those with and without pathologically significant intrapulmonary haemorrhage.

Results—Nasal haemorrhage was reported in 60 of 385 cases (15%) whose parents were interviewed. Pathologically significant intra-alveolar pulmonary haemorrhage was found in 47% of 115 cases studied, but was severe in only 7%. Infants with nasal haemorrhage had more haemorrhage into alveoli and air passages than age matched cases without nasal haemorrhage. In multivariate analysis, nasal haemorrhage was associated with younger infant age, bed sharing, and the infant being placed non-prone to sleep. Intrapulmonary haemorrhage was associated with the same three factors in univariate analysis, but in multivariate analysis only younger infant age remained statistically significant. There was no significant association between nasal or intra-alveolar haemorrhages and intrathoracic petechiae.

Conclusions—Nasal and intrapulmonary haemorrhages have common associations not shared with intrathoracic petechiae. Smothering is a possible common factor, although is unlikely to be the cause in most cases presenting as SIDS.

Keywords: sudden infant death syndrome; infanticide; nasal haemorrhage; pulmonary haemorrhage

Fresh haemorrhage at various anatomical sites is observed frequently in infants who have died suddenly and unexpectedly. When the usual widely accepted criteria are applied, the majority of these deaths will be diagnosed as sudden infant death syndrome (SIDS). Some cases with this diagnosis will have been smothered by another person either accidentally (overlaying) or intentionally (imposed suffocation). Petechial haemorrhages on the visceral pleura, epicardium, and capsule of the thymus are the most common sites of fresh haemorrhage in SIDS; in some studies petechiae have been found at one or more of these sites in more than 90% of cases. Intrapulmonary haemorrhage is also common in SIDS and may be intra-alveolar and/or into the respiratory passages. Intrapulmonary haemorrhage was observed microscopically in 66% of the more than 700 SIDS cases in the National Institute of Child Health and Human Development Co-operative Epidemiological Study.

Most intrapulmonary haemorrhage is trivial and in small amounts is difficult to distinguish from artefacts caused by handling of the lung at autopsy or during the preparation of histological sections. Potter et al found some intra-alveolar haemorrhage in more than 95% of 151 cases of SIDS, but considerable haemorrhage in less than 27%. Infants dying suddenly and unexpectedly are often found with fresh haemorrhage or blood stained secretions about the nose or mouth, but the incidence is not well documented.

There has been recent interest in such haemorrhages and reopening of debate on the terminology used for sudden infant deaths because of the suggestion that frank nasal haemorrhage or the more severe degrees of intrapulmonary haemorrhage might be markers for either accidental or imposed smothering. Meadow reported that of 70 children whose parents had been legally convicted of causing their deaths, 27 (39%) at death had frank blood apparent in the mouth, nose, or on the face. Bleeding from nose and/or mouth was reported in 11 (29%) of 38 children with apparent life threatening events in which suspicion of abuse was confirmed in the majority by covert video surveillance.

Becroft and Lockett have suggested that intrapulmonary haemorrhage might also occur during non-fatal episodes of imposed suffocation and that evidence at autopsy of previous intrapulmonary haemorrhage in the form of intra-alveolar iron containing macrophages (siderophages) might indicate that the later death was caused by imposed suffocation.

Potter et al found significantly more intra-alveolar haemorrhage in babies dying from deliberate or accidental suffocation than in SIDS but also found that there was more haemorrhage in the younger SIDS deaths and in co-sleeping deaths. Yukawa et al quantified intra-alveolar pulmonary haemorrhage in sudden infant death by digital image analysis. They concluded that even a moderate degree
(quantified as at least 5% affected) of pulmonary parenchymal haemorrhage may be an indicator of airway obstruction, either from overlaying or imposed smothering and that a diagnosis of SIDS may be inappropriate in such cases. They found that eight of 11 cases (73%) in which overlaying was admitted or a strong possibility showed more than 5% alveolar haemorrhage. Berry et al critically reviewed the paper by Yukawa et al and concluded that more than 5% alveolar haemorrhage was neither a necessary nor a specific criterion for the diagnosis of deliberate suffocation. He noted that these co-sleeping deaths occurred in younger infants and that further work was needed to establish whether young age or co-sleeping, or both, are independent variables accounting for the excess of pulmonary haemorrhage.

The epidemiology of nasal haemorrhage in SIDS has not been reported. Therefore, we have examined the incidence and epidemiological associations, including age and co-sleeping, of reported nasal haemorrhage in cases diagnosed as SIDS in the New Zealand Cot Death Study. In a subgroup of these cases we have made a semiquantitative assessment of the amount of intrapulmonary haemorrhage, correlated this with the occurrence of nasal haemorrhage, and examined the same epidemiological associations. We have compared the results with the epidemiology of intrathoracic petechial haemorrhages in SIDS as previously reported for the same population.

Materials and methods
The New Zealand Cot Death Study has been fully described previously. It was a large multicentre case control study of infants who died of SIDS between 28 days of age and the completion of their first year of life (postneonatal deaths) in the period 1 November 1987 to 31 October 1990. Approximately four weeks after death, a structured questionnaire was administered to parents by trained interviewers and obstetric records were also examined. Information was obtained on selection effects (age of infant, region, season, and time), sociodemographic background (marital status, occupation, age mother left school, and age of mother), pregnancy variables (parity, age of mother at first pregnancy, attendance at antenatal clinics, and education classes), infant factors (sex, birth weight, and gestation), and postnatal factors (admission to neonatal unit, sheepskin bedding use, breast feeding, maternal smoking, and infant sharing a bed with another person). The definitions of most of these variables have been presented previously. The data on nasal haemorrhage are based on a question referring to the death scene “Was there blood round his/her nose?” The response was categorised as present or not and no further questions on the severity of haemorrhage, character of the blood, or associated oral bleeding were asked.

Over the period of the study, there were 716 postneonatal deaths in the six study regions. There was a final diagnosis of SIDS with or without additional abnormalities in 485 (68%) of these deaths (3.5 per 1000 live births). Parental interviews were completed in 393 SIDS cases (81%) and obstetric records were examined in 465 (96%). Postmortem examinations had been performed in 475 (98%) of the SIDS cases. A total of 1800 controls were selected but this population is not relevant to the present study. The postmortem examination protocol and diagnostic criteria for SIDS have also been described previously.

Petechial haemorrhages were recorded in three categories: nil, few, and many at three sites: the visceral pleura, the thymic capsule, and epicardium.

Assessment of pulmonary haemorrhage and intralveolar siderophages
Histological sections of the lungs from 123 cases from two study regions had been stained previously by haematoxylin and eosin and for ferric iron by Perls’ reaction as part of a reported study of intra-alveolar pulmonary siderophages. One hundred and fifteen cases had sections of satisfactory quality for assessment of intrapulmonary haemorrhage. Eighty-six cases were from one region in which the sections were identified as from the left upper and right lower lobes respectively; the 29 cases from the other region had three to six sections taken from unspecified lobes of both lungs. The severity of haemorrhage into alveoli or into airways (bronchi and bronchioles) was assessed separately on a semiquantitative 0, 1, 2, 3 scale by one observer (DMOB). In this scale 0 represented no intraluminal red blood cells or numbers not distinguishable from artefact, and 1–3 represented increasing numbers of foci in which alveoli were largely filled with red cells or numbers of airways occupied at least in part by aggregated red cells. The 2–3 categories for intra-alveolar haemorrhage corresponded approximately to the “moderate” and “severe” categories illustrated by Yukawa and colleagues, which in subjective assessments by several pathologists had correlated in most cases with an assessment by image analysis of more than 5% of lung affected. In each case mean scores per section examined were derived separately for intra-alveolar and airway haemorrhage. Intra-alveolar haemorrhage was considered to be pathologically significant when there was a mean score of 1 or greater. Parents of 20 of the 115 SIDS cases that were assessed for intrapulmonary haemorrhage, reported nasal haemorrhage. These were compared with 20 age matched cases with no nasal haemorrhage with the observer blind to the nasal haemorrhage status. The remaining 95 cases without nasal haemorrhage were assessed later with no knowledge of other variables. The number of intra-alveolar siderophages had been assessed previously on a semiquantitative 0–3 scale for each section.

Analysis
The variables listed in table 1 were compared in SIDS cases with and without reported nasal haemorrhage. Univariate analysis of differences was carried out by $\chi^2$ statistics and calculation of odds ratios. Multivariate analysis was
Table 1 Number (percentage) of cases with and without nasal haemorrhage by risk factors and univariate* and multivariate† odds ratios (95% confidence intervals)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No haemorrhage</th>
<th>Nasal haemorrhage</th>
<th>Univariate OR (95% CI)</th>
<th>Multivariate OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of infant (weeks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;13</td>
<td>44 (22.1)</td>
<td>155 (77.9)</td>
<td>3.02 (1.64, 5.56)</td>
<td>2.95 (1.53, 5.68)</td>
</tr>
<tr>
<td>13+</td>
<td>16 (8.6)</td>
<td>170 (91.4)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>6 (8.6)</td>
<td>64 (91.4)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Middle</td>
<td>25 (14.5)</td>
<td>147 (85.5)</td>
<td>1.81 (0.71, 4.64)</td>
<td>1.55 (0.58, 4.19)</td>
</tr>
<tr>
<td>Low</td>
<td>29 (20.3)</td>
<td>114 (79.7)</td>
<td>2.74 (1.08, 6.95)</td>
<td>2.36 (0.86, 6.63)</td>
</tr>
<tr>
<td>First attendance at antenatal clinic (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>48 (18.0)</td>
<td>218 (82.0)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>4+</td>
<td>12 (10.7)</td>
<td>100 (89.3)</td>
<td>0.55 (0.28, 1.07)</td>
<td>0.38 (0.18, 0.82)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European and others</td>
<td>23 (12.1)</td>
<td>167 (87.9)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Maori</td>
<td>36 (21.1)</td>
<td>135 (78.9)</td>
<td>1.94 (1.10, 3.43)</td>
<td>1.60 (0.69, 2.69)</td>
</tr>
<tr>
<td>Pacifican</td>
<td>1 (4.3)</td>
<td>22 (95.7)</td>
<td>0.33 (0.04, 2.57)</td>
<td>0.17 (0.02, 1.52)</td>
</tr>
<tr>
<td>Position placed to sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prone</td>
<td>27 (11.0)</td>
<td>219 (89.0)</td>
<td>0.39 (0.22, 0.67)</td>
<td>0.50 (0.26, 0.94)</td>
</tr>
<tr>
<td>Non-prone</td>
<td>33 (24.3)</td>
<td>103 (75.7)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Position found</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prone</td>
<td>35 (13.0)</td>
<td>235 (87.0)</td>
<td>0.45 (0.25, 0.82)</td>
<td>0.45 (0.25, 0.82)</td>
</tr>
<tr>
<td>Non-prone</td>
<td>23 (24.7)</td>
<td>70 (75.3)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Bed sharing in the last sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28 (30.8)</td>
<td>63 (69.2)</td>
<td>3.62 (2.04, 6.45)</td>
<td>2.45 (1.16, 5.21)</td>
</tr>
<tr>
<td>No</td>
<td>32 (10.9)</td>
<td>261 (89.1)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Other variables analysed and found not to have any significant relation were region, time of death, season, marital status, age mother left school, age of mother this pregnancy, age of mother first pregnancy, parity, antenatal education, maternal smoking, sex, birth weight, gestation, admission to neonatal unit, breast feeding, dummy usage, illness, thermal insulation.
†Multivariate odds ratios control for other variables in the table with the exception of position found.

Results

Epidemiology of Nasal Haemorrhage

Nasal haemorrhage was reported in 60 (15.6%) of the 385 cases in which this information was recorded. Table 1 presents factors found to be associated (p < 0.1) with nasal haemorrhage in the univariate analysis and the results of placing these factors in logistic regression. In logistic regression, only younger infant age of less than 13 weeks (p = 0.001), being placed to sleep in a non-prone position (p = 0.031), sharing a bed with an adult (p = 0.19), and early attendance at antenatal clinics (p = 0.013) continued to show a statistically significant relation with nasal haemorrhage. Position placed to sleep and not position when found dead was used in multivariate analysis because this showed a stronger relation at the univariate level and is more reliably reported.
Sudden infant death syndrome

There were no significant associations between the finding of nasal haemorrhage and the number of either pleural (p = 0.52) or thymic (p = 0.15) petechiae; although there was an association with epicardial petechiae (p = 0.04) a test for trend showed no effect (p = 0.27). There were no significant relations between intra-alveolar haemorrhage and petechiae at any of the three sites (for thymus, p = 0.26; epicardium, p = 0.16; and pleura, p = 0.23).

Five of the 115 cases had diffusely distributed intra-alveolar siderophages in numbers which might cause suspicion of previous imposed suffocation, but only one had associated nasal haemorrhage; this was also the only case with a mean score for intra-alveolar haemorrhage greater than 1. Seventeen cases had small numbers of focally distributed siderophages not involving all sections of the lungs and only five of these were from the 20 cases with nasal haemorrhage. These findings do not suggest a relation between the presence of siderophages and nasal or pulmonary haemorrhage.

Discussion

These acute haemorrhages in SIDS are assumed to be agonal, part of the process of dying, and therefore their pathogenesis may be unrelated to the largely unknown mechanisms leading to these deaths. Further assumptions might be that the haemorrhages at each site would share some pathogenetic factors arising agonally and that there would be few, if any, associations with earlier events, including the known risk factors for SIDS. However, our previous study of the epidemiology of intrathoracic petechial haemorrhages showed, in multivariate analysis, that the number of petechiae at one or more intrathoracic sites was influenced by a wide range of demographic and prenatal/postnatal environmental factors, including some known risk factors for SIDS, and that there were differences suggesting a different pathogenesis at each site.

In the present study we have examined the same epidemiological risk factors as were investigated previously in relation to petechial haemorrhages; after multivariate analysis four factors—younger infant age, being placed to sleep in the non-prone position, sharing a bed with an adult, and early attendance at antenatal clinic—showed a statistically significant relation with nasal haemorrhage. The first three factors were also associated with intra-alveolar pulmonary haemorrhage in univariate analysis, but only younger infant age remained statistically significant in multivariate analysis. These results contrast with those of our previous study of intrathoracic petechiae. The only shared associations are between the non-prone sleeping position and increased pleural petechiae (in multivariate analysis, p = 0.058) and at the univariate level between bed sharing and increased thymic petechiae. There was an association between infant age and thymic petechiae but in the reverse direction—that is, there was a higher incidence in older infants. Conversely, we had shown strong associations between an infant being found with the head covered at death and epicardial and thymic petechiae, but in the present study no associations have been found between head covering and either nasal or pulmonary haemorrhages. These comparisons suggest a relation between the pathogenesis of nasal and intrapulmonary haemorrhages in SIDS which is not shared with intrathoracic petechiae. A common pathogenesis is supported by our further finding that infants with reported nasal haemorrhage had significantly more severe intrapulmonary haemorrhage than an age matched group with no nasal haemorrhage. Berry has suggested that the association could be because the nasal blood has been transmitted from the respiratory passages and is not a local phenomenon. However, transmission from the lungs appears unlikely to be the usual cause of nasal haemorrhage as only a minority of such cases in our study had severe intrapulmonary airway haemorrhage and another minority had no accompanying airway haemorrhage.

There has been little speculation on the causes of pulmonary and nasal haemorrhage in SIDS, in contrast with multiple theories of causation of intrathoracic petechiae. For petechial haemorrhages both systemic and local factors have been invoked; for example, the possible systemic effects on vascular integrity of hypoxia, microbial toxins, hyperthermia, and CO₂ rebreathing, or of transient hypertension increasing transcapillary pressure in either the pulmonary or systemic circuits, or of transient hyperthermia increasing transcapillary pressure in the lungs or nose, but the di differences in epidemiological associations suggest that other factors are required to explain the effects of age, bed sharing, and sleep position on the incidence of pulmonary and nasal haemorrhage. Accidental or intentional smothering could have a higher incidence in cases with nasal or intrapulmonary haemorrhage than in the much larger number with petechial haemorrhages, but this is unlikely to explain all the differences. The age distribution of known cases of imposed suffocation, both fatal and non-fatal, spans that of SIDS and has a similar bias towards younger infants. Bed sharing also is more common in younger SIDS cases. However, an exceptionally high incidence of accidental or imposed suffocation in apparent SIDS cases less than 13 weeks old would be required to explain an incidence of nasal haemorrhage more than twice that in older infants. We have shown that there is an association between bed sharing and nasal haemorrhage independent of age which might be
explained by deaths from overlaying. Again, this is unlikely to be the only explanation because nasal haemorrhage was found in 31% of those who had bed shared, and this is higher than most estimates of the contribution of overlaying to the well established risk of bed sharing for sudden infant death.23 The associations shown between the non-prone position when the infant was put to sleep and nasal, intrapulmonary, and petechial haemorrhages are unexplained.

An argument against nasal and pulmonary haemorrhages being strong markers for smothering is the frequency of these haemorrhages in sudden infant deaths. Fifteen per cent of SIDS cases in the New Zealand Cot Death Study had reported nasal haemorrhage at a time when the incidence of SIDS was high in New Zealand (3.5 per 1000 live births in the study period)13; this is well above previous estimates of the frequency of undiagnosed smothering. In the CESDI study the regional panel thought some 6% of deaths certified as SIDS were a result of maltreatment.25 In that study, when the SIDS rate had fallen and was much lower, the prevalence of nasal haemorrhage in non-prone infants, who were sleeping alone, was 13%, which is very similar to our study.26 However, the true incidence of imposed suffocation is unknown and may possibly be higher than some estimates. Also if a reliable distinction could be made between frank nasal haemorrhage and blood stained nasal secretions, the former might have stronger associations with smothering. We found intra-alveolar haemorrhage of some degree in 47% of the SIDS cases studied; therefore this also is not a useful marker.

The more severe intra-alveolar haemorrhage found in 7% of our cases was usually accompanied by nasal haemorrhage and corresponded to the more than 5% involvement of the lung considered suspicious of smothering by Yukiwa and colleagues.10 Further study is required to establish whether such severe pulmonary haemorrhage, or frank nasal haemorrhage are markers for smothering, particularly in older infants. At best, the haemorrhages would be a cause for suspicion only and not be diagnostic of smothering, a distinction emphasised previously for the significance of abundant intra-alveolar siderophages in the lungs as a marker for previous smothering.27

Severe fresh haemorrhage and moderately abundant siderophages were found with similarly low incidences in the lungs of the present series and together in only one case, but the numbers are too small to exclude an association.

In summary, we have found that infants with a diagnosis of SIDS who have reported nasal haemorrhage have more severe intrapulmonary haemorrhages than those without nasal haemorrhage, and that cases with nasal haemorrhage and/or pulmonary haemorrhage are younger than those without. Those with nasal haemorrhage were more likely to have bed shared and to have been placed to sleep in the non-prone position. Both nasal and intrapulmonary haemorrhage may be more frequent in deaths caused by imposed or accidental smothering than in deaths attributed to SIDS, but these haemorrhages are common in SIDS and smothering is unlikely to be the cause in the majority.

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