Epidemiology of apparent life threatening events

U Kiechl-Kohlendorfer, D Hof, U Pupp Peglow, B Traweger-Ravanelli, S Kiechl

Aims: To investigate the epidemiology and risk factors of apparent life threatening events (ALTE).
Methods: A prospective study enrolled all live-born infants in the Tyrol (1993–2001). Information on pregnancy, sociodemographic characteristics, child care practices, and infant’s behaviour in the first four to six weeks of life was collected with a standardised questionnaire, and was available for 44 184 infants. ALTE was identified from hospital admission records.
Results: During the study period 164 ALTE cases were identified, corresponding to an incidence of 2.46/1000 live births. In 73 of these infants no cause for the event and no comorbidity could be found (idiopathic ALTE). On average ALTE manifested ten weeks earlier than SIDS. Of various SIDS risk factors in the survey area, the prone sleeping position, smoking during pregnancy, low gestational age, profuse night sweating, and family history of infant death showed a moderate relation to the risk of overall ALTE, but only smoking maintained significance in the multivariate risk model. None of these variables was associated with idiopathic ALTE. In contrast to SIDS the frequency of ALTE did not change during the study period. None of the ALTE infants experienced SIDS later in life. Behavioural abnormalities such as feeding difficulties, episodes of pallor, cyanotic episodes, and repeated apnoea episodes were strongly associated with an increased risk of overall and idiopathic ALTE.
Conclusions: Although there are some similarities in the clinical presentation and epidemiology of SIDS and ALTE, differences clearly predominate. Accordingly, ALTE and SIDS should not be considered different manifestations of the same disease process.
such infants might be classified, and included the ICD-9 codes 798.4 (ALTE) and 786.0 and 786.9 (dyspnoea and respiratory abnormalities). In 2001 the ICD-10 classification was introduced, which no longer lists a specific ALTE code. Therefore, a search was made for R06.0 (dyspnoea), R06.8 (respiratory abnormalities, apnoea), and P28.4 (apnoea in the neonatal period). In a second step a definite classification was established by means of a critical review of the hospital medical records. To assess the incidence of ALTE the number of live births was used as the denominator. Associations between baseline variables and ALTE were analysed by means of the $\chi^2$ test. Relative risks were calculated by dividing the incidence of ALTE among infants with a potential risk condition by the incidence among those without. Multivariate relative risks were estimated by logistic regression modelling.

RESULTS

During the study period between 1993 and 2001 a total of 164 infants met the diagnostic criteria for ALTE, corresponding to a mean incidence of 2.46 per 1000 live births. There was no clear tendency of disease rates over the time period, especially no change parallel to the substantial drop in the SIDS rate after 1994 when the SIDS prevention programme was initiated in Tyrol (fig 1). Of note, none of the ALTE infants died from SIDS later in life. The median age-at-event for overall and idiopathic ALTE was 8 weeks compared to 18 weeks in SIDS infants ($p < 0.001$, Mann-Whitney U test). Age distributions are depicted in fig 2. Clinical comorbidity was detected in 91 of the 164 ALTE cases (55%). In descending order of priority, disturbances of the respiratory (29%) and the digestive tract (22%), congenital cardiac malformations (2%), inborn metabolic errors (1%), and convulsions (1%) were observed. In several infants ALTE was the initial clinical presentation of severe airway infection, especially respiratory syncytial virus bronchiolitis and pneumonia. Disturbances of the digestive tract included gastro-oesophageal reflux as well as aspiration or choking during feeding. In 73 infants no cause for the event and no concomitant disease were identified. These events were called “idiopathic ALTE”.

Potential association with SIDS risk factors was tested in 141 of the 164 ALTE cases (86%) for whom prospectively collected questionnaires were available. In the univariate analysis, ALTE was significantly associated with family history of infant death, single parenthood, profuse night sweating, as well as smoking during pregnancy (all $p < 0.001$), and less so with prone sleeping, low birth weight, or low gestational age. The latter associations lost significance once accounting for the multiple comparisons performed. In terms of absolute frequencies, the three main SIDS risk factors in the survey area (prone sleeping, lack of breast feeding, smoking in pregnancy) were much more prevalent among SIDS than ALTE infants. Of note, infant behavioural characteristics in the first weeks of life, such as repeated apnoeas and cyanotic episodes, a positive history of pallor, and feeding difficulties, were strongly related to the risk for ALTE. At least one of these characteristics was detected in about two thirds of infants who suffered an ALTE later on in life (66.4% vs 29.9% in controls; $p < 0.001$). The difference was even more pronounced when feeding difficulties were not included in the calculation (50.7% vs 16.9% in controls; $p < 0.001$). In a multivariate analysis allowing for all variables listed in table 1 (stepwise selection procedure with standard inclusion and exclusion criteria $p_E < 0.1$ and $p_C < 0.15$) the ALTE risk profile was composed of single parenthood, parent reported apnoeas, cyanotic episodes, episodes of pallor, feeding difficulties ($p < 0.01$ each), maternal smoking ($p = 0.036$), and family history of infant death ($p = 0.094$) (table 2).

When the analyses were restricted to cases of idiopathic ALTE, only behavioural characteristics qualified as significant risk indicators. Demographic characteristics and SIDS risk factors all did not achieve significance after accounting for the multiple comparisons performed (table 1) and did not enter the multivariate risk models (table 2).

DISCUSSION

Infants suffering from ALTE usually present with an acute and unexpected change in behaviour that alarmed the caregiver. The initial episodes can occur during sleep, when the infant is awake, or sometimes during feeding. The clinical appearance is defined by a combination of apnoea, colour change (cyanotic or pallid), marked change in muscle tone (limpness, rarely rigidity), choking, or gagging.1 Reuscitation may be necessary and range from mild stimulation to full cardiorespiratory support measures. ALTE is associated with or caused by a variety of diseases, but in 30–70%7–10 and 45% in our survey, the cause of the event remains undetermined and the event is then termed “idiopathic ALTE”.

![Figure 1](image1.png)

Figure 1  (A) Rates (per 1000 live births) and 95% CI of ALTE in Tyrol. (B) Rates (per 1000 live births) and 95% CI of SIDS in Tyrol.

![Figure 2](image2.png)

Figure 2  Age distribution of infants admitted to hospital with ALTE and those who died from SIDS, 1993–2001.
In various large population surveys, in which hospital records served as the source of information for case ascertainment, the frequency of ALTE was estimated to be between 0.46 and 10.0 per 1000 live births.\(^{11-14}\) The incidence of 2.46 per 1000 live births in our study fits very well into this range. Other evaluations, in which the ALTE classification relied on the parents’ response to questions such as whether they observed episodes of lifelessness or unusual respiratory events (apnoea, cyanosis, irregular respiration), reported incidence rates as high as 3–6%.\(^6\)\(^1\)\(^5\)

In contrast to SIDS, data on potential risk factors of ALTE are sparse. So far, only two prospective studies are available, one from Sweden\(^1\) and one from Tasmania.\(^4\) In the Swedish study, epidemiological features of SIDS cases and cases of an attack of lifelessness, which come close to our ALTE definition, were well documented, but comparable data were not available from healthy control infants in the same region.\(^1\) In the Tasmanian study the cohort cannot be regarded as representative of the general infant population, because only the one-fifth of live births with the highest SIDS risk scores were enrolled.\(^4\) Our study is the first prospectively designed and population based study to examine the epidemiology of ALTE, its potential relation to SIDS, and behavioural abnormalities.

### ALTE and SIDS

The relation between ALTE and SIDS is a matter of ongoing controversy. Similarities exist in the clinical appearance of both diseases. However, there are substantial differences in SIDS and ALTE epidemiology:

1. Intervention programmes aimed at reducing the prevalence of SIDS risk factors resulted in a substantial and sustained reduction of SIDS rates in the survey area of this study and several other countries.\(^1\)\(^9\)\(^-\)\(^11\) In contrast, over the same time period no consistent trends in the frequency of ALTE was observed (fig 1). In analogy, in Tasmania\(^2\) and New Zealand,\(^2\)\(^1\) where SIDS and total postneonatal mortality dropped dramatically following the initiation of SIDS intervention programmes, rates of hospital admission for apnoea/cyanosis did not change.

2. ALTE and SIDS, although both disorders of the first year of life, differed significantly in age-at-event, with ALTE manifesting 10 weeks earlier on average. The age distribution of both diseases in the Tyrol (fig 2) is similar to that in New Zealand.\(^2\)

3. The risk profiles for SIDS and overall ALTE showed only a modest overlap, and none of the various SIDS risk factors emerged as a significant predictor of idiopathic ALTE. In terms of absolute frequencies the three main SIDS risk variables in the survey area (prone sleeping, lack of breast feeding, smoking in pregnancy)\(^4\)\(^-\)\(^7\)\(^9\) were much more prevalent among SIDS than ALTE infants (table 1). Smoking in pregnancy was the only prominent SIDS risk condition that emerged as a significant risk predictor of

### Table 1 Association between various variables (demographic variables, infant’s characteristics, SIDS risk variables, behavioural characteristics) and ALTE

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls (%)</th>
<th>Overall ALTE (%)</th>
<th>p value</th>
<th>RR</th>
<th>Idiopathic ALTE (%)</th>
<th>p value</th>
<th>RR</th>
<th>SIDS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>50.9</td>
<td>45.0</td>
<td>0.166</td>
<td>0.79</td>
<td>40.4</td>
<td>0.113</td>
<td>0.65</td>
<td>50.0</td>
</tr>
<tr>
<td>Previous pregnancies ≥2</td>
<td>23.9</td>
<td>25.3</td>
<td>0.768</td>
<td>1.08</td>
<td>31.6</td>
<td>0.176</td>
<td>1.47</td>
<td>27.3</td>
</tr>
<tr>
<td>Educational level =12 years†</td>
<td>30.7</td>
<td>20.0</td>
<td>0.144</td>
<td>0.67</td>
<td>33.3</td>
<td>0.856</td>
<td>1.11</td>
<td>15.2</td>
</tr>
<tr>
<td>Single parenthood</td>
<td>9.6</td>
<td>23.8</td>
<td>&lt;0.001</td>
<td>2.93</td>
<td>16.4</td>
<td>0.089</td>
<td>1.84</td>
<td>9.5</td>
</tr>
<tr>
<td>Mother’s age &lt;23 years†</td>
<td>11.2</td>
<td>15.0</td>
<td>0.149</td>
<td>1.40</td>
<td>14.0</td>
<td>0.490</td>
<td>1.30</td>
<td>22.7</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>5.0</td>
<td>10.1</td>
<td>0.006</td>
<td>2.13</td>
<td>5.3</td>
<td>0.906</td>
<td>1.10</td>
<td>13.6</td>
</tr>
<tr>
<td>Family history infant death*</td>
<td>6.1</td>
<td>14.4</td>
<td>&lt;0.001</td>
<td>2.99</td>
<td>12.5</td>
<td>0.044</td>
<td>2.21</td>
<td>18.2</td>
</tr>
<tr>
<td>Low gestational age*</td>
<td>7.4</td>
<td>13.0</td>
<td>0.018</td>
<td>1.86</td>
<td>6.0</td>
<td>0.702</td>
<td>0.80</td>
<td>19.0</td>
</tr>
<tr>
<td>Smoking during pregnancy*</td>
<td>15.2</td>
<td>27.1</td>
<td>&lt;0.001</td>
<td>2.02</td>
<td>21.2</td>
<td>0.218</td>
<td>1.49</td>
<td>42.1</td>
</tr>
<tr>
<td>Prone sleeping position*</td>
<td>4.7</td>
<td>8.6</td>
<td>0.028</td>
<td>1.92</td>
<td>10.7</td>
<td>0.033</td>
<td>2.44</td>
<td>38.1</td>
</tr>
<tr>
<td>No breast feeding</td>
<td>10.5</td>
<td>14.9</td>
<td>0.092</td>
<td>1.90</td>
<td>9.1</td>
<td>0.740</td>
<td>0.86</td>
<td>55.0</td>
</tr>
<tr>
<td>Profuse night sweating*</td>
<td>11.2</td>
<td>22.9</td>
<td>&lt;0.001</td>
<td>2.33</td>
<td>17.5</td>
<td>0.131</td>
<td>1.68</td>
<td>35.0</td>
</tr>
</tbody>
</table>

### Table 2 Multivariate association between risk variables and overall and idiopathic ALTE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall ALTE RR (95% CI)</th>
<th>p value</th>
<th>Idiopathic ALTE RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single parenthood</td>
<td>2.2 (1.3 to 3.6)</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of infant death</td>
<td>1.7 (0.9 to 3.0)</td>
<td>0.094</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking during pregnancy</td>
<td>3.0 (1.1 to 2.6)</td>
<td>0.036</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeated apnoea episodes</td>
<td>7.0 (3.9 to 12.3)</td>
<td>&lt;0.001</td>
<td>10.0 (4.5 to 21.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Remarkably pallid</td>
<td>2.3 (1.3 to 4.1)</td>
<td>0.005</td>
<td>2.1 (0.9 to 4.9)</td>
<td>0.098</td>
</tr>
<tr>
<td>Cyanotic episodes</td>
<td>4.1 (2.3 to 7.2)</td>
<td>&lt;0.001</td>
<td>3.2 (1.4 to 7.6)</td>
<td>0.008</td>
</tr>
<tr>
<td>Feeding difficulties</td>
<td>2.2 (1.4 to 3.4)</td>
<td>&lt;0.001</td>
<td>2.5 (1.3 to 4.6)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Relative risks (RR) and 95% confidence intervals (95% CI) were estimated from logistic regression modelling. The multivariate analyses were fitted with a forward-stepwise selection procedure allowing for all variables in table 1 except for mother’s educational level which was available in a subgroup only. Seven and four variables, respectively, met the selection criteria (p value for entry: p<0.10, p value for removal: p>0.15).
What is already known on this topic

- SIDS prevention programmes have failed to reduce the frequency of ALTE

What this study adds

- This is the first large-scale prospective population-based study to examine risk factors for ALTE
- The study showed substantial differences in the epidemiology of ALTE and SIDS
- The majority of ALTE infants showed behavioural abnormalities in the first weeks of life

Summary

In our prospective evaluation a substantial proportion of infants with ALTE showed behavioural abnormalities such as repeated apnoeas, pallor, cyanotic episodes, and/or feeding difficulties prior to the ALTE event. Although there are some similarities in the clinical presentation and epidemiology of SIDS and ALTE, differences clearly predominate. Accordingly, ALTE and SIDS should not be considered different manifestations of the same disease process, nor can SIDS prevention programmes be expected to considerably lower the frequency of ALTE.

REFERENCES

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