Apparent Life-Threatening Events Could Be a Wake-Up Call for Sleep Disordered Breathing

Jole Rabasco, PhD, MD,1 Alessandro Vigo, MD,2 Ottavio Vitelli, PhD, MD,1 Silvia Noce, MD,2 Nicoletta Pietropaoli, MD,1 Melania Evangelisti, PhD, MD,1 and Maria Pia Villa, MD1*

Summary. Introduction: Polysomnographic recordings of children with an apparent life-threatening event (ALTE) have often displayed signs of partial or complete obstruction during sleep. Various studies have focused on facial dysmorphia in infants with ALTE and tried to establish a correlation between ALTE and obstructive sleep apnoea. Our study evaluates the phenotypic characteristics and the presence of sleep disorders in pre-school children who had at least one ALTE in the first year of life. Materials and Methods: We analyzed a group of pre-school children (mean age 5.21 ± 0.90 years) who were referred for an ALTE between 2008 and 2010. Children with no history of ALTEs were recruited as a control group. A detailed personal and family history was obtained for all the participants. Moreover, all the children underwent a general clinical examination and an ear, nose, and throat and orthodontic assessment. A clinical score was calculated according to the previously validated Sleep Clinical Record (SCR). Results: In the ALTE group (n = 107), snoring (25.2% vs. 6.1%), apnoeas (19.6% vs. 4.3%), restless sleep (31.7% vs. 6.1%), and habitual mouth breathing (35.5% vs. 12.2%, P < 0.05) were significantly more common (P < 0.05) than in the control group (n = 115). The ALTE group also displayed a higher frequency of Angle class II (27.1% vs. 15.7%, P < 0.05), narrow palate (72.9% vs. 51.3%, P < 0.05), and Friedman palate position (grades III–IV) (31.7% vs. 16.6%, P < 0.05) than the control group. Moreover, 38/107 (35.5%) children in the ALTE group had a positive SCR score compared with 14/115 controls (12.2%) (P < 0.05). Conclusions: Pre-school age children with previous ALTE had a higher frequency of sleep disordered breathing and malocclusion phenotypes. The occurrence of ALTEs may be predictive of the development of sleep disordered breathing and highlight the importance of a long-term follow-up. Pediatr Pulmonol.

Key words: infant pulmonary function; lung pathology; pulmonology (general); respiratory and airway muscle; sleep medicine.

Funding source: none reported.

INTRODUCTION

An apparent life-threatening event (ALTE) was defined by the National Institutes of Health Consensus Development Conference of Infantile Apnoea and Home monitoring in 1986 as an “episode that is frightening to the observer and that is characterized by some combination of apnoea (central or occasionally obstructive), color change (usually cyanotic or pallid), marked change in muscle tone, choking, or gagging.”

The episodes may occur during sleep, wakefulness, or feeding, and usually last a short time. Indeed, infants with such episodes are often asymptomatic upon presentation and the episodes usually resolve spontaneously.

ALTEs occur in 0.58/1,000 per live born infants and account for 0.6–0.8% of all emergency visits for children under 1 year of age.

In a recent review, Tieder et al.5 highlighted the need for a new definition because the one provided in 1986 is subjective and vague. The definition of the term ALTE...
should distinguish the description of symptoms from the
diagnosis; indeed, in approximately half of all the cases
diagnosed as ALTE, no apparent cause for the event has
ever been found. In the other half of the cases, a comorbid
condition is eventually identified (gastroesophageal
reflux, seizure, and lower respiratory tract infection).3,5–8

Polysomnographic recordings of children with ALTE
have often displayed signs of partial or complete
obstruction during sleep.9–11 Various studies have focused
on facial dysmorphia in infants with ALTE and tried to
establish a correlation between ALTE and obstructive
sleep apnoea (OSA).9,12 Indeed, children admitted to
hospital post-ALTE are reported to have a smaller
mandibular size if compared with controls.12 The reported
craniofacial phenotypes may contribute to intermittent
obstruction of the upper airway in some ALTE cases.
Guilleminault et al.13 investigated sleep disordered
breathing (SDB) and upper airway anomalies in first-
degree relatives of children with ALTE and found that
families of children with an obstructive SDB are
significantly more likely to include members with SDB
and with mild anatomic abnormalities involving the
craniofacial complex. They concluded that ALTEs may in
some cases be the first indication of a SDB syndrome and
that genotypes associated with upper airway dysmorphia
can result in an ALTE.

No epidemiological studies have previously evaluated
the clinical characteristics on a relatively large sample of
pre-school age children who had at least one ALTE in the
first year of life.

The aim of our study was to evaluate whether a group of
pre-school age children who have had at least one ALTE
in the first year of life, have a higher risk of developing
sleep disordered breathing than children in a control
group.

METHODS

We retrospectively analyzed a group of pre-school age
children who were referred for an ALTE in the first year of
life to the Pediatric Sleep Centres of Sant’Andrea
Hospital (Rome, Italy) and Regina Margherita Child
Hospital (Turin, Italy) between 2008 and 2010.

Three hundred and two eligible children were selected
on the basis of hospital records; 150 of these 302 children
were randomly selected while the remaining 107 agreed
to participate in the study and be re-evaluated in the
hospital setting 4–6 years after the first ALTE episode
(Fig. 1).

An ALTE was defined according to the definition of the
Consensus Conference held in 1986.1 Patients with genetic
disorders, cerebral palsy, neuromuscular diseases, major
craniofacial abnormalities, associated chromosomal syn-
dromes, maltreatment, or seizures were excluded.

After recruitment, a detailed personal and family
history was obtained for all the participants by means of a
questionnaire filled out by their parents. Moreover, all the
children underwent a general clinical examination and an
ear, nose, and throat (ENT), and orthodontic assessment.

A group of age- and sex-matched children with no
history of ALTE, according to the questionnaire filled out
by their parents, were recruited from a kindergarten as a
control group.

All the participants’ parents provided written informed
consent to the study. The study procedures were approved
by the hospital ethics committee.

Questionnaire Data

Information about the children’s family history
(presence of atopy, asthma, and OSA) and personal
history (birth weight, prematurity) was collected by
asking the participants’ parents to complete a question-
naire. The questionnaire also investigated the presence of
wheezing, rhinitis (presence of nasal obstruction, rhinor-
hea, sneezing, and nasal itching at least 4 days a week for
4 consecutive weeks), habitual mouth breathing, symp-
toms of gastroesophageal reflux (GER) in the first year of
life (suspected diagnosis by pediatrician).14

Moreover, the children’s parents were also asked to fill
in a questionnaire designed to investigate sleep symptoms
such as habitual snoring, witnessed apnoeic episodes,
frequent awakenings, or restless sleep.

Clinical Examination

A clinical score was calculated according to the Sleep
Clinical Record (SCR), a simple tool to screen SDB in
children that we had previously validated.15

The clinical examination included an ENT and
orthodontic assessment to detect the presence of nasal

ABBREVIATIONS:
ALTE apparent life-threatening event
BMI body mass index
ENT ear, nose, and throat
GER gastroesophageal reflux
OSA obstructive sleep apnea
SDB sleep disordered breathing

Fig. 1. Recruitment and exclusion of patients.
obstruction by considering: nostril patency; inferior turbinate hypertrophy; nasal septum deviation; tonsillar hypertrophy; dental/skeletal malocclusion; pathological palate position; narrow palate (constricted upper jaw and palate); presence of mouth breathing (detected by the Rosenthal and Glatzel tests).

Nostril patency was analyzed by blocking one nostril with one finger, inspiration through the non-occluded nostril, and repetition of the same manoeuvre with the other nostril. The manoeuvre was repeated three times.

Tonsillar size was graded according to a standardized scale ranging from 0 to 4. Tonsillar size was graded as: 1+ = medial borders of tonsils lateral to or extending to the pillars; 2+ = medial borders of tonsils lateral to or extending to the lateral uvular margins; 3+ = medial borders of tonsils medial to the lateral uvular margins; 4+ = includes “kissing” tonsils, which meet at the midline. We considered grades 3 and 4 as tonsillar hypertrophy.\(^{16}\)

The palatal position was graded according to Friedman classes, with a standardized scale ranging from 1 to 4.\(^{17}\)

All the children underwent an orthodontic examination to detect possible jaw deviation from normal occlusion. The malocclusion was classified according to Angle’s criteria.

**Class I**
The molar relationship of the occlusion is normal.

**Class II (Retrognathism, Overjet)**
The upper molars are not placed in the mesiobuccal groove but anteriorly to it. The mesiobuccal cusp usually rests in between the first mandibular molars and second premolars.

**Class III (Prognathism)**
The upper molars are not placed in the mesiobuccal groove but posteriorly to it. The mesiobuccal cusp of the maxillary first molar lies behind the mesiobuccal groove of the mandibular first molar. It is usually observed when the lower front teeth are more prominent than the upper front teeth.

Moreover, the presence of deep bite, open bite, and cross-bite must be evaluated, as must the presence of narrow palate (upper jaw and palate are constricted).

Deep bite is defined as an excessive amount of vertical overlap of the upper front teeth over the bottom front teeth.

In cross-bite, the upper posterior (back) teeth are in cross-bite if they erupt and function inside or outside the arch in the lower posterior teeth. Lower anterior (front) teeth are in cross-bite if they erupt and function in front of the upper anterior teeth. Cross-bite can involve either single teeth or groups of teeth.

Finally, open bite is a malocclusion in which teeth do not make contact with each other. With an anterior open bite, the front teeth do not touch when the back teeth are closed together. With posterior open bite, the back teeth do not touch when the front teeth are closed together.\(^{18}\)

A SCR score \( \geq 6.5 \) was considered positive.

The children’s body mass index (BMI) percentile was also recorded; obesity was diagnosed according to the International Obesity Task Force and was defined as greater than or equal to the 95th percentile of the BMI (pBMI).\(^{19}\)

### Statistical Analysis

Data are expressed as means ± SD. \( t \)-test, \( \chi^2 \) test, or logistic regression analysis were chosen when appropriate.

Differences were considered to be statistically significant when the \( P \)-value was \(<0.05\). All the statistical analyses were performed with the statistical software package (SPSS 21, Chicago, IL).

### RESULTS

One hundred and seven children with ALTE (mean age 5.21 ± 0.90 years, 44.9% males, mean BMI percentile 57.22 ± 31.91) and 115 controls (mean age 5.11 ± 0.64 years, 46.1% males, mean BMI percentile 59.09 ± 33.01) were enrolled. No differences in age, sex, BMI, or pBMI were found between the two groups. All the subjects were of Caucasian origin of middle socioeconomic status.

The mean age of the infants when the first ALTE occurred was 1.96 ± 2.03 months; 44.9% of the infants had more than one episode in the first year of life.

There were no significant differences in birth weight or prematurity between the ALTE and control groups. Smoking during pregnancy was reported in the mothers of 20/107 children (18.6%) in the ALTE group and of 8/115 (7%) in the control group (\( P < 0.05 \)) (Table 1).

A family history of snoring and OSA in parents or siblings was present in 62/107 (57.9%) of the children in the ALTE group and in 67/115 (58.3%) of the children in the control group, though the difference was not statistically significant.

No significant differences emerged between the two groups in their family history of atopy and asthma.

### TABLE 1—Personal History of Children in ALTE Group and Control Group

<table>
<thead>
<tr>
<th></th>
<th>ALTE group (n = 107)</th>
<th>Control group (n = 115)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity</td>
<td>17 (15.9%)</td>
<td>14 (12.2%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.10 ± 0.67</td>
<td>3.17 ± 0.55</td>
<td>0.89</td>
</tr>
<tr>
<td>Maternal smoking in pregnancy</td>
<td>20 (18.6%)</td>
<td>8 (7%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Wheezing</td>
<td>27 (25.2%)</td>
<td>15 (13%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>16 (15%)</td>
<td>18 (15.7%)</td>
<td>0.88</td>
</tr>
<tr>
<td>Symptoms of GER</td>
<td>56 (52.3%)</td>
<td>23 (20%)</td>
<td>0.000</td>
</tr>
</tbody>
</table>
As regards the clinical features, children with ALTE had a higher frequency of parent-reported symptoms of GER (52.3% vs. 20%, \( P < 0.05 \)) and wheezing (25.2% vs. 13%, \( P < 0.05 \)) (Table 1).

The participants’ parents filled out a questionnaire to evaluate night- and day-time symptoms of OSA. The ALTE group displayed a higher frequency of snoring (25.2% vs. 6.1%, \( P < 0.05 \)), apnoeas (19.6% vs. 4.3%, \( P < 0.05 \)), habitual mouth breathing (35.5% vs. 12.2%, \( P < 0.05 \)), restless sleep (31.7% vs. 6.1%, \( P < 0.05 \)), and night sweating (42.1% vs. 24.3%, \( P < 0.05 \)) than the control group. The ALTE group contained 6/107 (5.6%) children that had previously undergone an adenotonsillectomy compared with 2/115 (1.7%) in the control group (Table 2).

Children in the ALTE group, when compared with the control group, displayed a higher frequency of Angle class II (27.1% vs. 15.7%, \( P < 0.05 \)), narrow palate (72.9% vs. 51.3%, \( P < 0.05 \)), and Friedman palate position (grades III–IV) (31.7% vs. 16.6%, \( P < 0.05 \)) than the control group. The ALTE group contained 6/107 (5.6%) children that had previously undergone an adenotonsillectomy compared with 2/115 (1.7%) in the control group.

Finally, a logistic regression analysis was performed with a SCR positive score as the dependent variable, and sex, obesity, history of ALTE, prematurity, maternal smoking in pregnancy, wheezing, and GER as the explanatory variables. The only predictive variable in the model was a positive history of ALTE (\( P = 0.0009 \); \( \beta \) coefficient = 1.2600; \( R = 0.193 \); \( OR = 3.52 \); 95%CI 1.678–7.404).

### DISCUSSION

Our study detected a higher prevalence of sleep disordered breathing and malocclusion phenotypes in a group of pre-school age children who had, in the first year of life, at least one ALTE compared with a control group. ALTE is not a well-defined entity and includes a heterogeneous group of patients. In a high percentage of cases, no apparent causes have been found.

Various studies have investigated a possible correlation between craniofacial characteristics and OSA in infants with ALTEs.

Guilleminault et al. detected nocturnal polygraphic recording abnormalities in 58.8% of a group of infants with ALTEs under 10 months of age. Two-thirds of these infants not only had clinical symptoms of SDB but also mild facial dysmorphias, such as a long face, retrusion of the mandible, a small triangular chin, low-placed hard palate that could be clearly seen at 6 months of age. They concluded that these dysmorphias should be considered as risk factors for sleep disordered breathing. In another study, Horne et al. demonstrated that infants with ALTE frequently assume a similar body posture, consisting of a hand-to-chin position that appears to create a jaw thrust. In keeping with these observations, our study showed a higher frequency of malocclusion, narrow palate, and habitual oral breathing in the group of pre-school age children who presented, in the first year of life, at least one ALTE when compared with a control group. All these findings are usually considered to be risk factors for OSA.

A number of studies have reported a relationship between malocclusion patterns and variations in the size and form of the oropharyngeal airway caused by palate and/or tongue position.

In particular, children with a Class II malocclusion have a narrower anteroposterior pharyngeal dimension, which can be specifically observed in the nasopharynx at the level of the hard palate and in the oropharynx at the level of the tip of the soft palate and the mandible. A relatively short and/or posteriorly placed mandible might force the tongue and the soft palate back into the pharyngeal space, thereby causing a reduction in oropharyngeal volume.

These children therefore, tend to use mouth breathing because of partially impaired nasal respiration function. However, it is not possible to define the primum movens; indeed, even the switch from a nasal to oronasal breathing pattern induces functional adaptations on dentofacial morphology (increase in total anterior facial height, vertical development of the lower anterior face,

### TABLE 2—Symptoms of OSA and Clinical Evaluation in ALTE Group and Control Group

<table>
<thead>
<tr>
<th></th>
<th>ALTE Group (n = 107)</th>
<th>Control Group (n = 115)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Habitual snoring</td>
<td>27 (25.2)</td>
<td>7 (6.1)</td>
<td>0.000</td>
</tr>
<tr>
<td>Apnoeas</td>
<td>21 (19.6)</td>
<td>5 (4.3)</td>
<td>0.000</td>
</tr>
<tr>
<td>Restless sleep</td>
<td>34 (31.7)</td>
<td>7 (6.1)</td>
<td>0.000</td>
</tr>
<tr>
<td>Night sweating</td>
<td>45 (42.1)</td>
<td>28 (24.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Nasal septum deviation</td>
<td>3 (2.8)</td>
<td>3 (2.6)</td>
<td>0.92</td>
</tr>
<tr>
<td>Inferior turbinate hypertrophy</td>
<td>60 (56.1)</td>
<td>49 (42.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Habitual mouth breathing</td>
<td>38 (35.5)</td>
<td>14 (12.2)</td>
<td>0.000</td>
</tr>
<tr>
<td>Tonsillar hypertrophy (grades III–IV)</td>
<td>27 (25.2)</td>
<td>25 (21.9)</td>
<td>0.56</td>
</tr>
<tr>
<td>Friedman palate position</td>
<td>34 (31.7)</td>
<td>19 (16.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Angle class I</td>
<td>73 (68.2)</td>
<td>93 (80.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Angle class II</td>
<td>29 (27.1)</td>
<td>18 (15.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Angle class III</td>
<td>5 (4.7)</td>
<td>4 (3.5)</td>
<td>0.65</td>
</tr>
<tr>
<td>Narrow palate</td>
<td>78 (72.9)</td>
<td>59 (51.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>SCR positive score (≥6.5)</td>
<td>38 (35.5)</td>
<td>14 (12.2)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

*Pediatric Pulmonology*
maxillo-mandibular retrusion), which in turn create a vicious circle.23–26

The risk of developing malocclusion is greater when there is long-term exposure to an unbalanced muscular function due to mouth breathing.27

Mouth breathing clearly makes an environmental contribution to the etiology of such malocclusions since genetic factors play a major important role in facial growth and development.27

For these reasons, it is not unreasonable to suppose that ALTEs may be predictive of the future development of OSA. Guillemainault and Stooohs28 performed a 1-year follow-up study on a small group of infants with ALTEs and demonstrated that ALTEs may predispose subjects to OSA during early childhood.

In a previous study on the sleep cyclic alternating pattern (CAP) in infants with ALTE, Miano et al.13 showed that the obstructive apnoea/hypopnoea index was higher in such infants than in controls. Although we did not perform a polysomnographic analysis in the present study, we did ask the children’s parents to fill out a questionnaire in order to establish the presence of symptoms of OSA. Our data show that the frequency of night-time symptoms of OSA, such as snoring, apnoeas, restless sleep, and night sweating, was higher in the ALTE group than in the control group, as confirmed by a higher percentage of children with a positive SCR score in the former.

The logistic regression analysis indicated that a history of ALTE is a greater risk factor for SDB in pre-school age than sex, obesity, prematurity, maternal smoking in pregnancy, wheezing, or GER. When we evaluated the presence of GER symptoms in the first year of life, we detected a positive history of GER in 52.3% of the children in the ALTE group. The presence of GER is very common in infants with ALTEs, with the incidence in different studies ranging from 32% to 89%.5,29

As regards the mothers’ smoking habits, smoking during pregnancy was reported in 20/107 children (18.6%) in the ALTE group and in 8/115 (7%) of the children in the control group (P < 0.05). It has been demonstrated that foetal exposure to nicotine not only induces brain growth restriction associated with foetal hypoxia, but also affects brain development, as shown by changes in the nAChR subunit expression pattern in the foetus.30

A number of studies have shown that nicotine may alter autonomic nervous system function in infants prenatally exposed to tobacco smoke.31 Lavezzi et al.32 reported an altered expression of the neuromodulator substance P (SP) in the area of the trigeminal nucleus (TrN) in the dorsolateral part of the medulla as well as in the rostral spinal cord in infants who were victims of SIDS, especially in those with smoking mothers.

Experimental studies on rodents have shown that the TrN is involved in a range of rhythmic activities, such as suckling, mastication, swallowing, and breathing; it plays a fundamental role in the network that controls oral breathing and in the regulation of upper airway patency.33–36

One limitation of our study is that we performed a clinical and anamnestic evaluation without a polysomnographic study. The main strength of the study is the long-term follow-up if compared with previous studies.

In conclusion, our epidemiological study shows a higher frequency of SDB and craniofacial abnormalities in pre-school age children with a history of ALTEs. These findings suggest that ALTEs may be predictive of the subsequent development of SDB and highlight the importance of investigating the presence of SDB in a long-term follow-up.

In the light of these results, we recommend that when a child has one ALTE in the first year of life, the general pediatrician should investigate the presence of symptoms and clinical findings that are suggestive of OSA by means of simple questionnaires.15,37,38

AUTHORS’ CONTRIBUTION

Prof. Maria Pia Villa conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. Alessandro Vigo and Silvia Noce carried out the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted. Jole Rabasco, Ottavio Vitelli, Melania Evangelisti, Nicoletta Pietropaoli designed the data collection instruments, coordinated, supervised the data, critically reviewed the manuscript, approved the final manuscript as submitted. All the authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

REFERENCES

6 Rabasco et al.


