www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2021;10(2):e100207
doi: 10.7363/100207
Received: 2021 Feb 03; revised: 2021 May 04; accepted: 2021 May 09; published online: 2021 Jun 04

Original article

# Relationship between laryngomalacia and sleep-related breathing disorders in infants with brief resolved unexplained events

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## Abstract

**Introduction:** Brief resolved unexplained events (BRUE) occur during infancy. It is characterized by one or more symptoms, including skin color change, shortness of breath and unresponsiveness. Laryngomalacia is the most frequent cause of stridor in infants and results in the collapse of the supraglottic structures during inspiration and intermittent obstruction of the upper airways. To our knowledge, the relationship between BRUE and laryngomalacia has been little investigated.

**Methods:** The medical records of 448 children (age < 12 months) treated for BRUE between July 2011 and March 2018 and followed up until March 2020 were retrospectively reviewed. Endoscopic evaluation was performed using a flexible fibrolaryngoscope. All patients underwent a brief polysomnography and 24-h cardiorespiratory monitoring. Cardiorespiratory and oxygen saturation monitoring was continued at home; 94% of patients underwent follow-up.

**Results:** Laryngeal fiberoptic endoscopy revealed laryngomalacia in 11% of children with a clinical history of BRUE. Laryngomalacia was associated with obstructive/mixed apnea in 67%. Home cardiorespiratory monitoring showed a gradual reduction in the number of respiratory events during follow-up and complete resolution of laryngomalacia in 88% of patients.

**Conclusions:** This is the first report that showed follow-up data from cases of BRUE with laryngomalacia. The improvement in laryngomalacia alone, although not complete, was sufficient to improve obstructive events.

### Keywords

Laryngomalacia, brief resolved unexplained event, obstructive sleep apnea, children.

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### How to cite

Nosetti L, De Bernardi F, Sica E, Latorre P, Agosti M, Castelnuovo P, Cocciolo G, Zaffanello M. Relationship between laryngomalacia and sleep-related breathing disorders in infants with brief resolved unexplained events. J Pediatr Neonat Individual Med. 2021;10(2):e100207. doi: 10.7363/100207.

### Introduction

Brief resolved unexplained events (BRUE), previously termed apparent life-threatening events (ALTE) [1], is characterized by one or more symptoms including change in skin color, shortness of breath and poor responsiveness. Several potentially dangerous but treatable conditions are associated with ALTE. It can be triggered by a variety of gastrointestinal, neurological, respiratory, cardiovascular, metabolic and endocrine disorders among others [2].

BRUE is not a specific diagnosis but rather a sudden, short and spontaneously resolved unexplained episode in children under the age of 12 months. The cause of BRUE in infants is heterogeneous, making diagnosis often difficult on initial presentation [1, 3]. Episodes can sometimes resolve quickly and spontaneously without the need for intervention or may require immediate attention from the observer and intensive care if severe. The term BRUE should be applied only when the child is asymptomatic and no explanation for the episode can be gained from medical history and clinical evaluation [1, 3]. In 2016, the subcommittee on apparently threatening events of the American Academy of Pediatrics proposed the new term, BRUE, and recommended that the term ALTE no longer be used [3]. High-risk infants are younger than 2 months of age, have a history of prematurity (higher in infants of less than 32 weeks' gestation), and a history of more than one event [4]. The Italian guidelines recommend the use of the term BRUE only when referring to mild, idiopathic cases and the use of the acronym ALTE for severe cases that are unexplainable after first and second level examinations [5].

In 2019 Merritt et al. proposed a tiered approach for clinical evaluation and management of higher risk infants who have experienced BRUE. There are many potential causes of higher risk BRUE. History and physical examination finding, may help guide clinicians in identifying specific concerning features, one of these is laryngomalacia [4].

Laryngomalacia is the most frequent cause of stridor in newborns (prevalence 45-75%); it causes collapse of the supraglottic structures during inspiration and obstruction of the upper airways [6-8]. Symptoms generally appear during the first year of life and peak in frequency at 6-8 months before resolving spontaneously around 12-24 months [9]. Laryngeal stridor is due to immaturity of the cartilage scaffold of the larynx. The flaccid larynx collapses inward over the vocal cords with each breath and causes airway obstruction. The clinical manifestation of laryngomalacia is heterogeneous; it may be asymptomatic or severe, leading to insufficient growth, feeding difficulties, lung aspiration and obstructive sleep apnea (OSA) [10, 11]. Management of severe symptoms will entail a multidisciplinary team approach (otolaryngologist [aka ear, nose, and throat – ENT – doctor], neonatologist, sleep pediatrician, pediatric surgeon [for tracheoesophageal anomalies], gastroenterologist [for gastroesophageal reflux – GER], and geneticist) [7, 10, 12, 13]. Flexible fiberoptic laryngoscopy (FFL) is the procedure of choice for the direct visualization of the larynx [10, 14].

To our best knowledge, the relationship between BRUE (and ALTE) events and laryngomalacia has been little investigated to date [15-17]. Okada et al. reported only 2 cases of laryngomalacia among 69 infants with ALTE over a 10-year period. Laryngomalacia was diagnosed with the aid of a laryngoscopy; however, the number of children involved in the survey was not reported [15]. Willis et al. performed a 10-year retrospective, observational study on 1,148 infants with a history of ALTE and evaluated in a pediatric ENT service. The indications for ENT consultation were

gasping, stridor, and aspiration. 471 took part in a 5-year follow-up (inclusion criteria). Nine of 471 ALTE patients underwent a microlaryngoscopy. Only 3 patients were referred to the pediatric ENT service during initial admission and 6 were seen only later in childhood. Finally, only 3 patients were diagnosed with laryngomalacia [16]. In another study in infants (n = 128; 0.5-124.2 month-olds), both ALTE and snoring predicted high-airway abnormalities (n = 10, 7%) during laryngoscopy [17].

## Aims

To date, laryngomalacia is diagnosed in a select number of children with ALTE or BRUE at initial presentation, and extensive evaluation is not performed.

To clarify these issues, we performed a retrospective study reviewing the medical records of patients presenting at our institution because of ALTE or BRUE and, after careful ENT evaluation, diagnosed with laryngomalacia including investigation for sleep disordered breathing and GER comorbidities.

## Methods

### *Study design*

This is a retrospective monocentric observational study.

### *Study population*

We reviewed the medical records of children (age < 12 months) with ALTE or BRUE evaluated at our institution between July 2011 and March 2018 and followed up until March 2020.

Only patients with FFL-confirmed laryngomalacia and with a respiratory sleep study were included in the study. The following clinical data, also extracted from the records, were investigation for sleep breathing disorders, respiratory symptoms and underlined GER. In particular, we included children with ALTE or BRUE at initial presentation who underwent the FFL study and polysomnography. FFL was also used to investigate indirect laryngeal signs of GER.

ENT specialists and pediatricians evaluated the children at the Center for Respiratory Sleep Disorders, ASST Seven Lakes Pediatric Clinic, Varese, Italy.

### *ENT evaluation*

ENT evaluation is performed after BRUE diagnosis and risk stratification with careful history and physical examination in higher-risk infants. If no explanation is identified through the initial tier evaluation (ECG, hematocrit, blood glucose, continuous pulse oximetry), ENT evaluation and full polysomnography are indicated. FFL is performed by a pediatric otolaryngologist (F.D.B.) assisted by a nurse. Small babies are placed in upright position, the nurse holds the baby's head steady, and the caregiver restrains the child's arms. Pulse oximetry is used and oxygen and aspiration tubes are on hand. No general sedation is administered. Local anesthesia with 2% lidocaine is given only in children with a tiny nasal cavity. FFL evaluation is performed using a Pentax flexible fibrolaryngoscope and a Storz-equipped column with a light source, a camera, a monitor, and a recording system. The portable column allows FFL examination in the Neonatal Intensive Care Unit when needed. Otherwise, all procedures were carried out in a pediatric otolaryngology facility in a children's hospital by certified pediatric advanced life support medical staff, with an emergency room available as a safety precaution. The flexible fiberscope is inserted into the nostril and advanced through the nasal cavity to assess choanal patency. The instrument is then pushed toward the nasopharynx, the oropharynx, and the larynx to examine its conformation.

There are many classifications of laryngomalacia and all are based on morphological features [18, 19]. Evaluation of the larynx discloses the anatomical site of the collapse and identifies redundant mucosa of the aryepiglottic folds with collapse inward during inspiration (posterolateral), short aryepiglottic folds with curled tubular epiglottis (complete), and posterior collapse of the epiglottis on inspiration (anterior). Collapse of multiple secondary sites is often present [19, 20].

### *Full polysomnography*

All patients underwent a brief 2-h polysomnography (nap study) with E-Series PSG Compumedics that included a stable REM phase of at least 15% of sleep. The parameters were: thoracic and abdominal movement, oronasal flow, blood oxygen saturation ($SpO_2$), end-tidal carbon dioxide ($EtCO_2$), electroencephalogram (EEG), electrooculogram (EOG), electrocardiogram (ECG),

electromyogram (EMG), audio and video monitoring, and position sensor. Measurement of pH or pH impedance was performed in children with suspected GER. Some centers use daytime testing in young infants, who will sleep and be fed during the daytime and at night [21].

Apnea is classified as OSA or central sleep apnea or both. Based on the mean apnea-hypopnea index (AHI) score, the severity of sleep breathing problems was classified as mild (AHI 1-5 events/h), moderate (AHI 6-10 events/hour), and severe (AHI > 10 events/h) [22].

*Management and follow-up*

All patients were involved in at least a 2-year follow-up. The follow-up included FFL, dietary-behavioral counseling, and home cardiorespiratory monitoring. Home monitoring enables the detection of central apnea and/or intermittent hypoxemia [5]. Cardiorespiratory monitoring was performed at home with a Getemed Vitaguard® VG 3100 monitor (Getemed, Teltow, Germany) equipped with data recording of thoracic impedance and blood oxygen saturation (pulse oximetry). The data were periodically downloaded to the computer and the records were analyzed using VitaWin® software by an expert physician (LN) for central apnea (> 20 s), desaturation ($SpO_2$ < 90%), and bradycardia or tachycardia events.

Home monitoring was performed for at least 6 weeks. If an anomalous event occurred, monitoring was continued until the event had resolved. Preterm infants with BRUE were monitored up to 43 weeks of post-conceptional age. If symptoms persisted, monitoring was continued for another 6 weeks until complete resolution. Parental compliance was very important because they reported the child's symptoms over 24 hours.

The ethics committee of ASST Settelaghi, Varese, Italy approved the study (approval date 28.08.2018, no. 110/2017). Informed consent was obtained from the children's parents or caregivers.

## Results

*Patients*

Of the 448 patients admitted for BRUE or ALTE during the study period, 51/448 (11.4%; 57% female, 43% male) were diagnosed with laryngomalacia.

*Symptoms and associated conditions*

In children with laryngomalacia, inspiratory stridor was reported by parents and established in 31/51 (60.8%), tirage in 5 (9.8%), and pectus excavatum in 4 (7.8%). Diet-related symptoms were seen in 31 children (60.8%); GER was associated with laryngomalacia in 26 (51%) children (**Tab. 1**).

*Fiberoptic endoscopic findings*

The morphological subtypes of laryngomalacia were: redundant mucosa of the aryepiglottic folds with inward collapse on inspiration in 30/51 (58.8%) (posterolateral collapse), short aryepiglottic folds with curled tubular epiglottis in 16/51 (31.4%) (complete collapse), and posterior collapse of the epiglottis on inspiration in 5/51 (9.8%) children (anterior collapse).

*Type of sleep apnea*

The 51 patients with laryngomalacia were classified according to the most frequent types of

**Table 1.** Clinical characteristics of the study population (n = 51).

| Respiratory symptoms | No. | % |
|---|---|---|
| OSA and mixed sleep apnea | 34 | 66.7 |
| Respiratory stridor | 31 | 60.8 |
| Tirage | 5 | 9.8 |
| Pectus excavatum | 4 | 7.8 |

| Comorbidities | No. | % |
|---|---|---|
| Congenital cardiopathies [a] | 10 | 19.6 |
| Secondary airway lesions | 2 | 3.9 |

| Feeding problems | No. | % |
|---|---|---|
| GER | 26 | 51 |
| Regurgitation and belching | 25 | 49 |
| Hiccups | 19 | 37.3 |
| Choking during the meal | 14 | 27.5 |
| Vomiting | 12 | 23.5 |
| Prolonged feeding time, altered suction ratio, deglutition-respiration, dysphagia | 10 | 19.6 |
| Cough during the meal | 9 | 17.6 |

[a] Patent foramen ovale (PFO), interatrial defect (IAD), and interventricular defect (IVD).
GER: gastroesophageal reflux; OSA: obstructive sleep apnea.

apneas found on polysomnography. OSA were more frequent in 20/51 (39.2%), the mixed apneas were more frequent in 14/51 (27.5%), and the central apneas were more frequent in 17 (33.3%) children. Based on AHI criteria, sleep disordered breathing severity was mild in 14 (27.5%), moderate in 30 (58.8%), and severe in 7 (13.7%) children.

*Management*

All patients with laryngomalacia followed a behavioral dietary therapy and 27/51 (52.9%) were treated with drugs. In particular, 8 (15.7%) children were treated with histamine (H2) inhibitors or proton pump inhibitors (PPIs) and 19 (37.3%) with alginates. Only 1 underwent surgical treatment of the laryngomalacia with supraglottoplasty, due to persistent and very noisy breathing. Among children with respiratory symptoms, 8 (15.7%) were treated with nasal wash hypertonic solutions, nasal drugs (steroids) or oral antibiotics if indicated (upper respiratory tract infections).

*Follow-up*

The follow-up was carried out in 48/51 (94.1%) children. Three children did not come to the scheduled checkup. In these children, home cardiorespiratory monitoring disclosed a gradual reduction in the number of desaturation events. The mean duration of follow-up was 9.8 months (range, 2-31) with a mean healing time of 12.5 months (range 1-31). Complete resolution of laryngomalacia was observed in 45 (88.2%) children.

## Discussion

In total, 1 in 9 children with ALTE or BRUE events had laryngomalacia. The anamnestic interview revealed that 60.8% of these children had at-home respiratory stridor. In a subsequent evaluation, OSA and GER were the most frequent comorbidities associated with laryngomalacia. At the end of home follow-up monitoring, respiratory events improved in all children; however, laryngomalacia did not resolve in 11.8% of children. This is the first report that shows that in infants with ALTE or BRUE there is an improvement in laryngomalacia, together with sleep disordered breathing reduction.

Diagnosis of laryngomalacia relies on visualization of the larynx during breathing. Evaluation can be done in patients who are awake or with the help of anesthesia/sedation [20, 23]. Evaluation of laryngomalacia with FFL is more accurate if performed during anesthesia/sedation than in the patient who is not awake (100% sensitivity and 100% specificity vs. 93% sensitivity and 92% specificity, respectively) [14]. We evaluated the larynx in conscious children. Vigilance tests are easier to perform for extensive screening. We performed morphological classification of the larynx. Other morphological classification systems have been proposed such as that of Holinger and Konior, which is based on 5 types of laryngomalacia [9]. The University of Groningen recently proposed another classification of laryngomalacia that distinguishes only 3 purely dynamic morphological types [19]. However, we prefer to use an anatomical classification because it better reflects the endoscopic collapse of the supraglottic structures and is more appropriate when deciding which type of supraglottoplasty to perform.

Although a wide range of conditions can mimic ALTE (e.g., child abuse, congenital anomalies, epilepsy, innate errors of metabolism and infection), the risk of a recurrent or serious event is extremely low. The rationale to replace the term ALTE with that of BRUE was to improve the quality of care [3]. Because laryngomalacia has been studied relatively rarely as a cause of ALTE, the relationship between the two is still unclear. Furthermore, otolaryngologists are infrequently consulted to examine children with ALTE. Airway abnormalities are considered rare in these children [16], yet our data suggest a possible relationship between BRUE and ALTE events, laryngomalacia and OSA. We recently reported that laryngomalacia (20.3%) and GER (50.8%) were frequently observed in 48 BRUE and 11 OSAS infants (< 1-year-old) with upper respiratory tract obstruction [24]. ENT assessment should be considered in patients with BRUE and when there is suspicion or indirect signs of GER. The Italian guidelines recommend second level ENT assessment with FFL in patients with a history of ALTE/BRUE [5].

We performed FFL assessment for BRUE in all children < 12 months of age. Laryngeal stridor was present in 60% and the incidence of OSA was very high. We found that laryngomalacia was strongly associated with OSA and that it may contribute significantly to OSA in these children [24]. Digoy et al. reported that laryngomalacia may contribute significantly to OSA in children >

12 months of age [25]. Katz et al. reported that a body growth defect, hypoxemia, OSAS or other complications may be present in 20% of children with laryngomalacia [26]. Gonçalves et al. found that most patients with laryngomalacia also had central apnea, while those with other laryngeal problems did not have a predominant type of apnea [27]. Furthermore, a study carried out at the Cincinnati Children's Hospital Medical Center in 2014 confirmed the prevalence of central apnea in children with laryngomalacia [28]. In these children, the laryngeal tone and the sensorimotor integrative function of the larynx were altered. GER, neurological diseases, and low Apgar scores can influence the severity of the disease and its clinical course [11].

ALTE and BRUE are a challenge for the clinicians. In children with laryngomalacia, OSA without declared history of ALTE or BRUE events was recently established as being common (77.4%) [29]. Recently, in a retrospective review of 102 infants with concomitant laryngomalacia and sleep-related breathing disorders, 55.9% had only OSA and 44.1% had both central sleep apnea and OSA that progressively improved over time [30]. The comorbid OSA and central sleep apnea improved together with laryngomalacia, according to the study by Ratanakorn et al. [30]. All previous studies did not specifically mention that these children experienced ALTE or BRUE events. In BRUE patients aged between 1 and 12 months both laryngomalacia and GER were frequently diagnosed [24]. However, BRUE had more referred-by-parents' sleep symptoms than controls [31].

The relationship between ALTE or BRUE and GER is debated. On one hand, the guidelines of the National Institute for Health and Care Excellence (NICE) confirm that GER is only very rarely the cause of apnea or ALTE [5]. On the other hand, respiratory tract infections and GER are reported to be a more common diagnosis among patients with BRUE [32].

The novelty of our study is that, after careful investigation, laryngomalacia was frequently observed in infants with ALTE or BRUE events and with OSA and GER comorbidities. We cannot prove that laryngomalacia is a possible cause or risk factor of ALTE or BRUE events. To resolve this issue, we would need to compare the frequency of this anomaly in a group of healthy children including the investigation for OSA and GER as possible comorbidities. However, this investigation is ethically unthinkable. Therefore, 75.7% children with laryngomalacia had baseline abnormal swallowing functions [10] and oropharyngeal dysphagia with aspiration was the most common diagnosis identified in infants presenting with ALTEs. Observed clinical feedings incorrectly identified 26% of patients as having no oropharyngeal dysphagia when in fact they had aspiration [33]. Interestingly, in our series of children with BRUE (61%), eating disorders were present in a mild form, including regurgitation and hiccups.

The overall incidence of GER was 60%. Most of the children with laryngomalacia also had GER [10, 34]. A systematic review of the literature reported the frequent coexistence of acid reflux and laryngomalacia. Although the definition of reflux differed across studies, the overall prevalence was high (59%). The authors concluded, however, that the evidence for a causal association was limited [34]. In another study, GER was observed in 64% of patients and was significantly associated with severe symptoms [35]. GER is frequently encountered in children; it can be an accidental finding or related to OSA in children with BRUE. In early infancy (0-18 months), daily GER symptoms were present in more than a quarter of children but then declined in frequency and almost completely disappeared by the age of 12 months [36]. In our study, GER was present in half of the patients, more than that reported by Katz et al. [26], which suggests a possible comorbidity in infants with associated laryngomalacia and BRUE. Moreover, 23.5% of the children had comorbidities attributable to heart disease or secondary upper airway injury. In a previous study involving 110 patients, 27% had comorbidities such as congenital and/or vascular heart disease (1.7%), hereditary or perinatal neurological disease (10.9%), and genetic disorders (14.5%) [37].

Home monitoring can detect intermittent apnea and/or hypoxemia, which can compromise the integrity of the central nervous system. In 1986, the U.S. National Institutes of Health (NIH) Consensus Conference indicated home monitoring in children with severe ALTE, idiopathic ALTE, and siblings of sudden infant death syndrome (SIDS) victims [38]. This recommendation is included in the guidelines of the Italian Society of Pediatrics [5]. We monitored the BRUE patients for apnea and desaturation and performed FFL to evaluate progression of laryngomalacia until resolution of respiratory events. All patients who completed the follow-up showed a gradual reduction in the number of night desaturations until complete resolution.

To our best knowledge, home cardiorespiratory monitoring is not recommended for the follow-up of children with laryngomalacia alone [7, 9, 13]. Children with mild laryngomalacia can be managed with close clinical observation. Continuous monitoring of severe laryngomalacia is necessary, however, because symptoms may worsen with the natural course of the disease [6]. Severe signs, present in 10% of children with laryngomalacia, are dyspnea with intercostal or xiphoid retraction, OSA, and/or inhalation episodes during meals or feeding difficulties [39]. However, laryngomalacia and GER are associated with OSA in young children (age < 1 year) [24]. Home monitoring has been generally recommended only for patients with a history of ALTE but not for the prevention of cardiorespiratory events in children with laryngomalacia alone [39].

In conclusion, FFL demonstrated the presence of laryngomalacia in 11.4% of children with a clinical history of high risk for BRUE. BRUE is a heterogeneous condition, in which laryngomalacia should be considered. The present study is the first to involve children under the age of 12 months with BRUE and laryngomalacia and OSA and GER highly present as a comorbidity. Laryngomalacia should always be evaluated because, although subclinical in some cases, it can be a risk factor or a possible cause of BRUE in children.

## Conclusions

In conclusion, laryngomalacia was diagnosed in 1 out of 9 of our children presenting with ALTE or BRUE. FFL in patients with a clinical history of ALTE or high risk of BRUE may contribute to the diagnosis of laryngomalacia. In these children, sleep apneas and GER were strongly concomitant conditions. Comorbid sleep disordered breathing was highly present, mainly of moderate severity, and GER was diagnosed in half of these patients. Eating disorders were present in more than half of these patients. The interrelationship between laryngomalacia, sleep apneas and BRUE requires further studies to confirm our observations.

## Declaration of interest

The Authors have no conflicts of interest to declare. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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