Does Reflux Have a Causative Role in Laryngomalacia?

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Introduction

Laryngomalacia is the most prevalent laryngeal anomaly in infants, with approximately 60% of cases of neonatal stridor attributable to this disorder [1]. As a pathologic condition, it is defined by abnormal laryngeal dynamics in which supraglottic collapse occurs with inspiration. Although congenital in nature, it typically manifests in a delayed fashion, becoming most noticeable approximately 2-4 weeks after birth. This delayed phenomenon is poorly understood, but it may be in part due to the Bernoulli Effect produced by a natural increase in the respiratory flow rates of older infants, which then creates sufficient negative intra luminal pressure to cause collapse of a congenitally flaccid larynx.

Gastroesophageal reflux is a common finding in patients with laryngomalacia. Children with inspiratory stridor often have associated symptoms of frequent spitting and back arching, and treatment for reflux at times appears to alleviate the symptoms of inspiratory stridor. However, the clinical overlap of reflux induced airway obstruction and laryngomalacia makes it difficult to determine if reflux has a role in the development of laryngomalacia itself. GER has been implicated by association as a causative factor in a number of upper airway disorders such as chronic cough [2], chronic rhinosinusitis [3] and recurrent group [4]. Strong clinical evidence exists to support the role of GER in subglottic stenosis and surgical outcomes [5,6]; this is supported by an animal study by Little et al. that showed gastric acid application was significantly associated with the development of subglottic stenosis in a canine model [7]. In addition, both clinical and animal studies show that reflux can also cause laryngospasm, which may be an important mechanism in recurrent apneas and apparent life threatening events [8]. Not surprisingly, GER has also been implicated in the pathogenesis of laryngomalacia. The purpose of this review is to describe the different studies that argue for and against a causative role for GER in laryngomalacia.

Background

The variable collapse and vibration of supraglottic mucosa in laryngomalacia often results in a slightly lower pitched, fluttering stridor than that caused by glottic or subglottic pathology; however, the stridor produced can sometimes be higher pitched and non-fluttery, making it difficult to differentiate laryngomalacia from other causes of stridor on the basis of the sound alone. Symptoms are most noticeable during feeding or agitation, and in the supine position. With the exception of severe cases that result in failure to thrive or complications such as apnea and cyanosis, most cases of laryngomalacia do not require surgical treatment, and usually slowly resolve over the first year and a half of life [9]. Despite its clinical familiarity to every otolaryngologist, no consensus has been reached regarding the pathophysiology of laryngomalacia. Possible causes include neuromuscular, anatomical and histologic abnormalities, and it is also likely that a combination of etiologies may be present in certain individuals.

Central neurologic abnormalities are a common coexistent finding in children with laryngomalacia [10]; cases have also been described of patients that developed an acquired form of laryngomalacia after a neurologic insult, supporting neuromuscular immaturity or dysfunction as a contributory factor in at least some cases of laryngomalacia [11]. With regards to anatomical etiologies, traditional teaching describes the “omega-shaped” epiglottis as an important factor in the development of laryngomalacia; however, in our clinical experience and of others, this configuration is often seen in unaffected infants [12], supporting the principle that laryngomalacia is not a diagnosis based on anatomical findings, but one that can only be verified upon the visual confirmation of supraglottic collapse with inspiration. Common histological findings include subepithelial edema, lymphatic dilation [13] and chronic inflammatory changes [14]; however, the question remains unanswered whether these findings represent a histologic basis for laryngomalacia, or whether these are acquired changes caused by chronic supraglottic collapse and excessive mucosal vibration. Histologic examination of laryngeal cartilage has not been possible in most patients with laryngomalacia because of its characteristic benign clinical course. Shulman et al. performed a post-mortem evaluation of two tracheal specimens from two related individuals that suffered from a form of familial laryngomalacia that revealed some histologic abnormalities, namely hypercellularity and multiple abnormally enlarged lacunae [15]; however, since these individuals had a rare genetic laryngotracheal abnormality, we cannot use this finding as a basis to conclude that a chondropathy occurs in nonsyndromiclaryngomalacia. In fact, other histologic studies have not identified any cartilaginous abnormalities associated with laryngomalacia [13,16].

Laryngomalacia is definitively diagnosed by the visualization of inspiratory supraglottic collapse. This is easily accomplished by Flexible Fiberoptic Laryngoscopy (FEL), a commonly performed office procedure that can also exclude other laryngeal abnormalities such as vocal fold paralysis or glottic webs. Synchronous airway lesions do occur in up to 18% of infants with laryngomalacia, leading some otolaryngologists to recommend routine Direct Laryngoscopy and Bronchoscopy (DL and B) for all patients with this disorder; however, since only 3-4% of infants have a second airway lesion severe enough to warrant additional surgical treatment [17,18], DL and B should probably be performed selectively based on the severity and characteristics of an infant’s airway symptoms.

Different opinions exist regarding the definition of severe laryngomalacia and when surgical intervention is necessary; some of the more common indications used are failure to thrive, severe upper airway obstruction and frequent hospitalization [10]. Although early anecdotals reports described epiglottic surgery as a successful approach

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to laryngomalacia, tracheostomy was the traditional surgery of choice for severe cases until Lane et al. described the endoscopic excision of excess arytenoid mucosa in 1984 [19]. Since then, different series have shown that endoscopic supraglottoplasty is a well-accepted procedure with minimal morbidity/mortality that results in almost immediate improvement in symptoms [9,20,21]. However, surgical complications like supraglottic stenosis can occur in a minority of patients [22]. Although infrequent, the difficulty in the management of this complication has led some investigators to recommend unilateral supraglottoplasty as an initial alternative, with the option of a staged contralateral operation for persistent symptoms [23]. Either way, avoiding overaggressive removal of supraglottic tissue and preservation of an intact strip of interarytenoid mucosa are important surgical principles that can minimize the possibility of this complication. Other congenital anomalies such as Pierre-Robin sequence [22] or concurrent neurologic abnormalities [10] are also associated with a higher rate of post-operative complications after supraglottoplasty.

The objective evaluation of the choice and success rate of surgical and/or medical management of laryngomalacia depends on the faithful use of a classification system. Bauman and colleagues described a system separating laryngomalacia into three types that may occur independently or in combination: type 1- prolapse of arytenoid mucosa; type 2- lateral collapse caused by shortened aryepiglottic folds; and type 3- posterior epiglottic collapse [18]. This system's advantages are its simplicity and that a clear type of supraglottoplasty corresponds to each type: type 1- excision of excess arytenoid mucosa; type 2- release of aryepiglottic folds; type 3- epiglottopyexy.

Pro

Any attempt to address the possible relationship of GER to laryngomalacia is complicated by the observation that reflux alone can result in symptoms that closely mimic laryngomalacia [24,25]. Subtle differentiating characteristics of reflux-induced stridor (confusingly sometimes referred to as pseudolaryngomalacia) are reportedly a more variable temporal pattern and failure to improve with the prone position. Associated symptoms of frequent spitting up or the Sandifer position. Associated symptoms of frequent spitting up or the Sandifer syndrome (reflux associated back arching and/or torticollis) may also favor reflux-induced stridor over conventional laryngomalacia [26]; correlation of stridulous episodes with distinct reflux events identified during pH probe testing definitively confirms this diagnosis. Unfortunately, as in laryngomalacia, we have a poor understanding of the mechanism that underlies reflux- induced stridor. A strong case can be made for laryngospasm as at least one possible etiology for this disorder; Herbst et al. showed that esophageal instillation of acid in infants led to laryngospasm [27]. This is further supported by a canine study by Bauman et al. demonstrating reflux induced laryngospasm can occur through not only a direct laryngeal chemoreflex, but from distal esophageal afferent stimulation as well [8].

Of all major studies that have examined laryngomalacia and GER, none have conclusively demonstrated that treatment of GER significantly improved the resolution of laryngomalacia more than that which occurs with time alone. In a retrospective analysis of children who underwent single probe pH testing for otolaryngologic symptoms, Bouchard et al. showed that 61% of patients with a diagnosis of laryngomalacia had significant GER. They also found that four of five laryngomalacia patients treated medically for reflux had improvement in their upper airway symptoms. However, the symptoms that resolved were not defined, and as discussed above, the complexity involved in the separation of symptoms due primarily to laryngomalacia and those from concurrent GER makes it difficult to interpret this data. Was there an actual decrease in supraglottic collapse, or did medical treatment only improve simultaneous reflux-induced symptoms?

Besides reflux, central nervous system disease is another common finding associated with laryngomalacia. Belmont and Grundfast found that 23% of their patients with laryngomalacia also had neurologic abnormalities such as hypotonia, central apneas and developmental disorders [12]. In a retrospective series described by Senders et al., 52% of their patients who underwent supraglottoplasty for laryngomalacia had central nervous system disorders, while 47% had reflux disease present [10]. Halpern et al. addressed the relationship of neurologic disorders to GER in their study of 613 children referred to three different tertiary care centers for evaluation of reflux by single probe pH studies. They identified a statistically significant higher incidence of reflux disease in patients with central nervous system disease vs. those without CNS abnormalities (69% and 41% respectively) [28]. Although there appears to be a strong association between GER and central nervous system disease, no study has fully examined the relationship of both GER and neurologic abnormalities to laryngomalacia.

From a histopathologic standpoint, mucosal inflammation and edema from chronic exposure to refluxate has been proposed as a causative mechanism for GER in laryngomalacia. However, in a histological study of arytenoid mucosa in nine patients that underwent supraglottoplasty for severe laryngomalacia, Chandra et al. found surprisingly little of the mucosal/submucosal inflammation that would have been expected from reflux [13]. This finding occurred despite a 77% incidence of GER documented by pH probe and/or barium swallow, leading the authors to conclude that GER does not exacerbate or cause laryngomalacia through an inflammatory mechanism.

Although different investigators have described a high incidence of GER with laryngomalacia and postulated that GER can worsen or even initiate laryngomalacia by causing mucosal edema and inflammation, an opposite mechanism is equally possible- abnormal negative intrathoracic pressures caused by laryngomalacia can overwhelm the protective role of the lower esophageal sphincter, thus resulting in GER. An animal study by Wang et al. demonstrated that increasing degrees of upper airway obstruction caused a proportional increase in negative intrathoracic pressures [29]. The possibility that this mechanism translates into clinical GER in the setting of laryngomalacia is partially supported by a small prospective series described by Hadfield et al., in which patients who had single pH probe documented GER prior to supraglottoplasty for severe laryngomalacia experienced a statistically significant decrease in the severity of GER after surgery [30].

Finally, inconsistencies in diagnostic criteria and study design are a common limiting factor in many studies that have attempted to evaluate GER and its relationship to different otolaryngologic disorders. A meta-analysis by Rosbe et al. closely scrutinized all studies found in MEDLINE that examined upper airway pathology and reflux. They found significant deficits in most studies, including the lack of suitable controls, inconsistency in testing for GER and failure to identify confounding factors and their significance. Moreover, the comparison of data across studies was limited by the use of different definitions for pediatric GER, as well as the use of different diagnostic modalities across studies [31].

Con

Almost all reports of laryngomalacia include descriptions of associated GER and the importance of treating this aspect of this disorder. Different rates of associated GER reflux have been described, ranging from 23% to 80% [12,32]. The discrepancies in rates of
identified reflux in independent series may be a reflection of the inconsistent criteria used to diagnose laryngomalacia – ranging from the diagnosis of stridor alone to visual confirmation by FFL – as well as the different modalities used to assess GER. In brief, investigators have used different methods to evaluate GE reflux in part due to preference, but also because of technological limitations of different eras. Barium esophagrams and video swallow studies (although useful in evaluating the swallow mechanism and excluding problems with gastric emptying or esophageal motility) only examine swallowing and GE reflux in a discrete period of time, making it impossible to definitively rule out the absence of reflux. Bronchoscopy with bronchoalveolar lavage for lipidladden macrophages can evaluate the possibility of reflux-associated aspiration. A Colombo Index > 70 indicates aspiration, but does not differentiate secondary aspiration due to reflux from primary aspiration with swallowing [33]. Esophageal or post- cricoid biopsies are other informative procedures also easily performed at the time of DL and B. Intraepithelial eosinophils or basal epithelial zone hyperplasia confirm the presence of esophagitis, but these findings can be due to primary eosinophilic esophagitis as well as reflux induced inflammation [34]. Although single probe esophageal pH probe monitoring has been the traditional method used to document esophageal acid exposure, dual pH probe testing has emerged as the method of choice to evaluate both GER and laryngopharyngeal reflux. Despite this, upper probe normative values and a true reflux index have not yet been defined for the pediatric population [35]. A promising new modality is intraluminal impedance measuring, which measures changes in esophageal impedance from the passage of a bolus. While normative pediatric data has not been established, its main advantage over pH probe monitoring is that it can also detect and quantify nonacidic reflux, a relatively uncharacterized phenomenon that may have a role in upper airway disease [36].

Bouchard described similar findings in their retrospective chart review, which identified a 61% incidence of reflux in patients with a diagnosis of laryngomalacia, though diagnostic criteria for laryngomalacia were not defined. Although four of five laryngomalacia patients were reported to have symptomatic improvement after medical treatment with prokinetic agents and H2 receptor antagonists, no comparison to a control population was performed to determine if this improvement was due to medical treatment of reflux, or if it was a result of the natural regression of laryngomalacia.

A retrospective study by Bibi compared the prevalence of reflux in patients who underwent bronchoscopy for chronic respiratory symptoms to a control population. The diagnosis of laryngomalacia was made after visual confirmation of severe epiglottic or arytenoid collapse. GER was evaluated by either barium swallow or by single probe pH study. Of the eleven children who were diagnosed with laryngomalacia, GER found in 63% of patients with this diagnosis, which was a statistically significant difference from the 39% incidence in their control population. Although controls were used in this study, criteria for the control population, such as age/gender matching or comorbid factors were not described.

A prospective study by Giannoni examined 33 children diagnosed with laryngomalacia. These children were evaluated by esophageal pH probe testing or barium swallow for reflux, and the results were used to calculate a graded GER severity score. In addition, patients were classified as having severe laryngomalacia if they had experienced one or more of the following complications: severe airway symptoms requiring hospitalization; failure to thrive; multiple pneumonias/rupper respiratory tract infections; and the necessity for surgical intervention. In their patients who underwent testing for reflux, they found a 65% incidence of high grade GER in patients with severe laryngomalacia vs. a 20% incidence in patients with mild laryngomalacia. However, since laryngomalacia severity was based on clinical criteria, it is difficult to separate symptoms caused by laryngomalacia from those that may be due to GER alone.

As discussed earlier, dual probe pH studies are now considered the gold standard for evaluation reflux and upper airway disease. Matthews et al. used 24-hour dual probe pH monitoring in a prospective evaluation of 24 children diagnosed with laryngomalacia. This diagnosis was based on history and symptoms, as well as the characteristic appearance of laryngomalacia as visualized by FFL. 100% of the infants studied had some degree of pharyngeal acid exposure during the study period. Interestingly, this occurred with a simultaneous 66% incidence of abnormal distal probe results, showing that significant laryngopharyngeal reflux can occur in the setting of normal lower probe findings. Although normative data for LPR in the pediatric population has not yet been established, children with laryngomalacia in this study had over an eight-fold increase in pharyngeal reflux episodes when compared to children without respiratory symptoms [35].

**Bottom line**

Despite differing methods and variable results, it is clear from the articles described in this review that gastroesophageal reflux is associated with laryngomalacia. However, we cannot conclude from these studies whether or not GER has a causative role in the development of laryngomalacia. Stridor, respiratory distress and failure to thrive can be caused by both disorders, making it impossible to definitively separate out symptoms due to reflux and those related to laryngomalacia. In addition, spontaneous improvement will occur in most cases of laryngomalacia with or without medical management of GER, which makes it difficult to determine whether medical treatment hastens the resolution of primary laryngomalacia symptoms, or if it just decreases symptoms related to GER alone.

This issue can only be properly addressed with randomized prospective trials that focus on the question of whether or not laryngomalacia improves with medical treatment of GER. This would also require standardization of diagnostic criteria for reflux and appropriate control populations. Since clinical conclusions based on symptoms are so difficult in this setting, defined classification schemes need to be used to define the character and degree of laryngomalacia in addition to a thorough description of laryngoscopic findings to help delineate the coexistence of GER laryngitis. An obstacle to this goal is the large sample size necessary to detect a statistical difference for a mostly benign disorder that typically spontaneously improves regardless of treatment. This could be addressed by a multi-institutional study, but since tertiary care centers would be chiefly be involved, this would need to take into account bias based on referral patterns. Finally, unlike other disorders like subglottic stenosis or laryngospasm, similar animal studies would be difficult in the evaluation of laryngomalacia, since it is a diagnosis based on laryngeal dynamics, and not on a specific anatomical or physiologic abnormality that can be objectively measured.

From a clinical standpoint, because of the current lack of data supporting a causative role for GER in laryngomalacia, simple observation should suffice for routine cases of laryngomalacia. However, if concurrent symptoms of frequent spitting up, back arching and apneic events are present, empiric treatment for GER is a reasonable option since current anti-reflux medication has relatively few risks and complications in otherwise healthy children. However,
in very young infants or children with significant medical problems, a thorough gastroenterology evaluation should be performed prior to medical treatment.

References


