Lack of Association Between Esophageal Biopsy, Bronchoalveolar Lavage, and Endoscopy Findings in Hoarse Children

David L. Mandell, MD; David J. Kay, MD; Joseph E. Dohar, MD; Robert F. Yellon, MD

Objective: To determine the prevalence of esophagitis (based on esophageal biopsy results) and aspiration (based on bronchoalveolar lavage [BAL]) in children with hoarseness.

Design: Retrospective medical chart review spanning 24 months of 127 consecutive children (mean age, 6.9 years; range, 1.8-17 years) who presented with hoarseness to 2 attending otolaryngologists.


Intervention: All subjects underwent direct laryngoscopy, rigid bronchoscopy with BAL, and rigid or flexible esophagoscopy with biopsy.

Main Outcome Measures: The BAL result was considered positive if the number of lipid-laden macrophages was "moderate" or "large," and the esophageal biopsy result was considered positive if any 2 of the following 3 histologic criteria were present: basal cell hyperplasia, increased papillary height, and intraepithelial inflammatory infiltrate. Comparisons between subjective endoscopic findings and objective test results were made using the t test and contingency table analysis, where appropriate.

Results: Of the 127 children, 104 (82%) had vocal nodules; 53 (43%) had endoscopically visualized laryngitis; 36 (28%) had tracheobronchial inflammatory changes; 60 (47%) had abnormal esophagoscopic findings; 47 (37%) had a positive BAL result; and 38 (30%) had a positive esophageal biopsy result. There was no significant correlation between BAL and esophageal biopsy results (P = .11). The odds of having positive BAL or esophageal biopsy results were unaffected by the presence of vocal nodules; endoscopically visualized inflammation of the larynx, trachea, or esophagus; or symptoms or previous clinical history of gastroesophageal reflux disease.

Conclusion: Positive esophageal biopsy and BAL results are prevalent among children with hoarseness, regardless of subjective upper aerodigestive tract endoscopic findings.

Arch Otolaryngol Head Neck Surg. 2004;130:1293-1297

THE INCIDENCE OF VOCAL quality disturbances in school-aged children is approximately 7%.1 Vocal nodules, the most common benign laryngeal mass lesions in childhood, are found in approximately 67% of hoarse children.2 In recent years, an association between gastroesophageal reflux disease (GERD) and laryngeal disorders has become the focus of intense study.3 However, there is no consensus on the most practicable and accurate technique for diagnosing GERD in children, and the existence of a relationship between laryngopharyngeal reflux and posterior laryngitis, silent aspiration, hoarseness, and vocal nodules in children has not been elucidated. The purpose of this study was to review the findings of upper aerodigestive tract endoscopy, including the results of tests for GERD and aspiration (esophageal biopsy and bronchoalveolar lavage), in consecutive children with hoarseness to determine whether there was any discernible association between esophageal biopsy and bronchoalveolar lavage (BAL) results on the one hand, and clinical history and subjective endoscopic findings on the other.

METHODS

Outpatient records from the Department of Pediatric Otolaryngology at Children's Hospital of Pittsburgh, Pa, were retrospectively searched.
using the International Classification of Diseases, Ninth Revision (ICD-9) codes for hoarseness (codes 478.5 and 784.49). The search period spanned 24 months, from October 31, 2000, to October 31, 2002. This study was granted an exemption from the hospital Human Rights Committee review under 45 Code of Federal Regulations 46.101(b)(4). Outpatient clinic notes and operative and histopathologic reports were reviewed.

To be included in the study, patients needed to have been diagnosed as having hoarseness, and to have undergone an operative workup that included all 3 of the following: direct laryngoscopy, with or without flexible fiberoptic nasolaryngoscopy; rigid bronchoscopy with BAL; and either rigid or flexible esophagoscopy with biopsy. Patients were excluded if the duration of hoarseness was less than 4 weeks and/or associated with a viral upper respiratory illness.

In our hospital, operative laryngoscopy was frequently performed because of cooperation problems with younger patients, and also because it allows immediate treatment of recurrent respiratory papillomatosis with impending airway obstruction; easy performance of simultaneous GERD and aspiration workup, including esophageal biopsy and BAL; and response to the frequent need for other simultaneous operative procedures, eg, tympanostomy tube placement or dental procedures.

Endoscopic images were viewed on a Sony HR Trinitron color video monitor (Sony Corp, Tokyo, Japan) using a Storz camera adaptor and a xenon light source (Karl Storz Endoscopy-America, Culver City, Calif); flexible fiberoptic nasolaryngoscopy was performed using a 4-mm Storz flexible laryngoscope to assess true vocal fold mobility; Storz rigid pediatric bronchoscopes and esophagoscopes cannulated with a 0° Hopkins rod telescope were used to perform laryngobronchoscopy and esophagoscopy; and BAL was performed by wedging a disposable flexible suction catheter through the bronchoscope under direct vision into a bronchus to the right lower lobe, followed by instillation into a suction trap and then aspiration of 1 mL/kg (up to 20 mL) of 0.9% sodium chloride solution. Two posterior wall mucosal biopsy samples were obtained from the endoscopically estimated distal third of the esophagus using optical biopsy forceps (Karl Storz, Tuttingen, Germany). Occasionally, flexible (rather than rigid) esophagoscopy with blinded grasp biopsy was performed through the scope (Olympus, Tokyo, Japan) by gastroenterology staff members.

A patient was considered to have symptoms of GERD if any of the following had been recorded preoperatively: burping, dysphagia, odynophagia, abdominal pain, heartburn, chronic cough, throat clearing, sore throat, or bad breath not associated with tonsillitis or sinusitis. The patient was considered to have a history of GERD if at any time in the past the diagnosis of GERD had been made.

Vocal nodules were defined as solid, white, nodular thickenings at the junction of the anterior and middle thirds of the membranous portion of one or both true vocal folds. Laryngitis was considered present if the operative report mentioned mucosal erythema and/or edema of any of the following sites: true vocal folds, arytenoids, and interarytenoid and postcricoid areas. Vocal nodules alone were not considered evidence of laryngitis. Abnormal bronchoscopic findings were considered present if any of the following tracheobronchial findings had been reported: mucosal cobblestoning, erythema, edema, and viscous secretions. Abnormal esophagoscopic findings were considered present if any of the following had been noted: mucosal erythema, edema, friability, nodularity, vertical banding, patulous appearance of the esophageal lumen, and presence of gross reflux.

Material obtained from BAL was routinely stained with standard oil red O and hematoxylin counterstain. The number of lipid-laden macrophages (LLMs) was described in the pathology department in our hospital makes the diagnosis of histologic esophagitis if at least 2 of the following 3 features are present: basal cell hyperplasia, increased papillary height, and epithelial inflammation with eosinophils, neutrophils, or lymphocytes. For the purpose of the study, the result of an esophageal biopsy was considered positive with 2 or 3 of these features; intermediate with only 1 of the features; and negative with none of the features.

Direct laryngoscopic, rigid bronchoscopic, and esophagoscopy observations were recorded from dictated operative reports in nonweighted fashion. Each BAL and esophageal biopsy specimen was analyzed by 1 of 6 nonblinded hospital pathologists.

Data were entered into an Excel 2002 spreadsheet (Microsoft Corp, Seattle, Wash), and analyzed with software packages SPSS, version 11.0 (SPSS Inc, Chicago, Ill) and STATA, version 8.0 (STATA Corp, College Station, Tex). Comparisons were made using the t test for continuous data and contingency table analysis for categorical data. Contingency tables were analyzed using χ² testing, and the Fisher exact test when expected values were 5 or less. Mantel-Haenszel estimates of the odds ratios were made to determine if confounding was present. A 2-sided a level of 0.05 was considered significant for all tests.

A secondary analysis was performed to determine if any risk factors for vocal nodules could be elucidated. The potential risk factors identified were age, sex, history of voice abuse, respiratory symptoms, symptoms and/or family history of GERD, abnormal bronchoscopic and/or esophagoscopic findings, and positive BAL and/or esophageal biopsy results. Contingency table analysis was performed as above, including Mantel-Haenszel estimates of the odds ratios. The results were confirmed with univariate logistic regression analysis, followed by the construction of a multivariate logistic regression equation.

RESULTS

Hoarseness had been diagnosed in 210 consecutive children over 24 months. Two otolaryngologists (J.E.D. and C.D.B.) saw 137 patients (65%) between them, while 5 other otolaryngologists saw the remaining 73 patients (35%). To decrease the variability of subjective documentation and management, only data concerning the 137 patients seen by the first 2 otolaryngologists were studied. Of these patients, 129 underwent upper aerodigestive tract endoscopy with BAL and esophageal biopsy. The 8 patients who did not undergo operative endoscopy either underwent office laryngoscopy or were lost to follow-up. After excluding 2 cases because of insufficient BAL specimens, the records of a total of 127 patients were studied.

Clinical and endoscopic data from the 127 children with hoarseness are listed in Table 1. The average age of the subjects was 6.9 years (range, 1.8–17 years), the male–female ratio was 1:4:1, and the median duration of hoarseness was 6 months (range, 1–120 months). A χ² contingency table analysis showed no significant correlation between BAL and esophageal biopsy results (P = .11).

As demonstrated in Table 2, the odds of a subject having a positive BAL or esophageal biopsy result were...
unaffected by the presence of vocal nodules; endoscopically visualized inflammation of the larynx, trachea, or esophagus; or symptoms or previous clinical history of GERD.

The endoscopic finding of laryngitis increased the risk of having vocal cord nodules 5-fold (odds ratio, 5.05; 95% confidence interval, 1.18–22.73; P<.01). Contingency table and univariate logistic regression analysis revealed no other endoscopic, pathologic, or clinical factors that were significantly associated with vocal nodules.

When grouped by age, there were no statistical differences in the prevalence of vocal nodules, endoscopic laryngitis, and positive BAL findings between children who were 2 to 4 years old, 5 to 11 years old, and 12 to 18 years old. However, 2- to 4-year-old and 12- to 18-year-old children had a significantly higher prevalence of positive histologic esophagitis (43% and 62%, respectively) than 5- to 11-year-old children (23%) (P<.05).

When grouped by endoscopic findings, the children with both vocal nodules and endoscopically visualized laryngitis (n=40) and children with neither vocal nodules nor endoscopically visualized laryngitis (n=10) seemed the most disparate. However, the prevalence of positive BAL results (38% and 30%, respectively) and of positive esophageal biopsy results (28% and 20%, respectively) were similar in the 2 groups.

It is generally believed that vocal nodules are due to mechanical phonatory trauma resulting from chronic voice abuse. Treatment with voice therapy can be effective, but many children demonstrate a lack of motivation for following vocal hygiene recommendations. Surgery is usually not recommended because of the risk of permanent vocal disability and nodule recurrence. Although most vocal nodules seem to resolve spontaneously after puberty, 11% of the patients with vocal nodules in the present study were between the ages of 12 and 18 years.

Gastroesophageal reflux has been implicated as a causal cofactor in many adult voice problems. Based on 24-hour dual (esophageal and hypopharyngeal) pH probe studies, GERD has been documented in up to 70% of adults with hoarseness10 and in 64% of adults with vocal nodules (vs 18% of adults without nodules).11

An association between hoarseness and GERD may also exist in children. In 1992, Putnam and Orenstein12 reported a case of a child with hoarseness and GERD whose hoarseness resolved with metoclopramide HCl and cisapride therapy. Subsequent studies using 24-hour distal esophageal pH probes have demonstrated an incidence of GERD of 62% among children with chronic hoarseness.2

Although esophageal and hypopharyngeal pH probe testing is considered the criterion standard for diagnosing GERD in adults, its role in pediatric GERD is less clear due to sampling error and lack of age-related definitions of “normal.” Esophagoscopy with biopsy is a valid alternative indicator of reflux esophagitis in children,13 and is a convenient way to diagnose GERD, especially if it is performed at the time of other operative procedures.14 In children, it has been shown that laryngeal biopsies with inflammatory changes correlate with changes in upper esophageal biopsies, but not with results of dual pH probe studies.15

Posterior laryngitis, a finding often ascribed to GERD, has been reported in up to 90% of children with hoarseness.16 However, posterior laryngitis is a diagnosis plagued by clinical subjectivity. By assigning weights to various inflammatory laryngoscopic findings, Belafsky et al10 devised an 8-item “reflux finding score,” which was significantly higher in adults with pH-probe-documented laryngopharyngeal reflux than in controls. A similar scoring system has not been devised for children. It is likely that tracheal findings thought to be related to GERD, such as mucosal cobblestoning, edema, and thick secretions, are not accurate enough indicators of GERD to be relied on for the diagnosis.17

Esophagoscopy findings thought to be demonstrative of GERD include friability, ulceration, edema, and erythema. However, histologic esophagitis has been demonstrated in only 45% to 71% of children with grossly abnormal mucosa on esophagoscopy.18,19 The incidence of histologic esophagitis in pediatric controls (aside from limited autopsy data) is unknown.11

The use of BAL in the workup of GERD is based on the theory that the presence of LLMs in bronchial washings may be an indicator of aspiration, and silent aspiration of food and gastric substances is felt to be relatively common in children with GERD.6 The presence

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Table 1. Clinical and Endoscopic Findings in 127 Children With Hoarseness

<table>
<thead>
<tr>
<th>Clinical and Endoscopic Findings</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td><strong>Demographic data</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>74 (58)</td>
</tr>
<tr>
<td>Female</td>
<td>53 (42)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
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<tr>
<td>&lt;2</td>
<td>1 (1)</td>
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<tr>
<td>2-4</td>
<td>47 (37)</td>
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<tr>
<td>5-11</td>
<td>66 (52)</td>
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<tr>
<td>12-18</td>
<td>13 (10)</td>
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<tr>
<td><strong>Clinical findings</strong></td>
<td></td>
</tr>
<tr>
<td>Symptoms suggestive of GERD</td>
<td>63 (50)</td>
</tr>
<tr>
<td>Previous diagnosis of GERD</td>
<td>22 (17)</td>
</tr>
<tr>
<td>Presently taking anti-GERD medica</td>
<td>5 (4)</td>
</tr>
<tr>
<td><strong>Laryngeal diagnoses</strong></td>
<td></td>
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<tr>
<td>Vocal nodules</td>
<td>104 (82)</td>
</tr>
<tr>
<td>Laryngitis</td>
<td>53 (42)</td>
</tr>
<tr>
<td>Both nodules and laryngitis</td>
<td>40 (32)</td>
</tr>
<tr>
<td>Normal-appearing larynx</td>
<td>6 (5)</td>
</tr>
<tr>
<td>True vocal fold polyp</td>
<td>2 (2)</td>
</tr>
<tr>
<td>True vocal fold paralysis</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Bronchoscopy and esophagoscopy results</strong></td>
<td></td>
</tr>
<tr>
<td>Abnormal bronchoscopy findings</td>
<td>36 (28)</td>
</tr>
<tr>
<td>Abnormal esophagoscopy findings</td>
<td>60 (47)</td>
</tr>
<tr>
<td>Positive BAL result</td>
<td>47 (37)</td>
</tr>
<tr>
<td>Positive esophageal biopsy result</td>
<td>38 (30)</td>
</tr>
<tr>
<td>“Intermediate” esophageal biopsy result</td>
<td>44 (35)</td>
</tr>
<tr>
<td>BAL and esophageal biopsy results both positive</td>
<td>18 (14)</td>
</tr>
<tr>
<td>BAL and esophageal biopsy results both negative</td>
<td>60 (47)</td>
</tr>
</tbody>
</table>

Abbreviations: BAL, bronchoalveolar lavage; GERD, gastroesophageal reflux disease.
of LLMs in BAL specimens has been demonstrated in 85% and 19% of children with and without documented GERD, respectively.20 Other studies have shown that patients with either clinical aspiration or documented GERD have significantly higher LLM semiquantitative indices than those without aspiration or GERD.4,6

There are several problems with the use of BAL in the workup of GERD and aspiration. First, since there is no criterion standard for the diagnosis of aspiration in children, the sensitivity and specificity of the test cannot be calculated.7 Second, other conditions besides aspiration (such as bronchial obstruction) may lead to phagocytosis of lipid by pulmonary macrophages and hence a false-positive result.21 Third, the finding of significantly elevated LLMs does not differentiate whether lipids, if aspirated, arrived in the lung directly, because of swallowing abnormalities, or secondarily because of GERD.22

The availability of a large number of hoarse, otherwise healthy children who had undergone upper aerodigestive tract endoscopic evaluation afforded an opportunity to study the association between hoarseness, GERD, and silent aspiration. The prevalence of positive histologic esophagitis (30%) was high compared with the known 5% prevalence of symptomatic GERD in healthy infants aged 10 to 12 months.22 However, true control data are lacking. In the present study of hoarse children, those aged from 5 to 11 years had a significantly lower prevalence of histologic esophagitis than younger and older cohorts, indicating that, for this age group, factors other than GERD (such as voice abuse) may be responsible for the development of hoarseness.

While no individual clinical factor or endoscopic finding was predictive of GERD, an assessment of multiple factors (patient history and endoscopy, BAL, and esophageal biopsy results) provided broader information about the possible presence of GERD. This information was useful in triaging hoarse children with vocal nodules to observation, speech therapy, antireflux medical therapy, or gastroenterology referral.

Pediatric office laryngoscopy can be a valuable diagnostic tool in hoarse children, and empirical antireflux medical therapy is a low-risk management option. However, operative endoscopy should still be considered if (1) GERD is strongly suspected, (2) patients are difficult to examine, (3) stridor or airway obstruction exists, and/or (4) children need general anesthesia for any other procedure in the near future.

The most significant limitation of the present study is its retrospective nature. It is possible that not all clinical and endoscopic findings, both positive and negative, were reported, and that differences in interpretation between observers could exist. In an attempt to reduce variability in reporting, data from only 2 otolaryngologists with similar practice patterns were studied. Data from 5 other otolaryngologists in our hospital were excluded, which introduces a potential source of bias.

Submitted for Publication: January 9, 2004; final revision received January 20, 2004; accepted May 14, 2004.

Correspondence: David L. Mandell, MD, Department of Pediatric Otolaryngology, Children's Hospital of Pittsburgh, 3705 Fifth Ave, Pittsburgh, PA 15213 (david.mandell@chp.edu).

Previous Presentation: This study was presented at the 19th Annual Meeting of the American Society of Pediatric Otolaryngology; Phoenix, Ariz; May 3, 2004.

Acknowledgment: We thank Charles D. Bluestone, MD, for providing subjects for the study and for his invaluable insight and guidance.

## REFERENCES