Laryngopharyngeal Reflux and Laryngeal Web Formation in Patients With Pediatric Recurrent Respiratory Papillomas

Bradford W. Holland, MD; James A. Koufman, MD; Gregory N. Postma, MD; William F. McGuirt, Jr., MD

Objective: To determine whether treatment of laryngopharyngeal reflux reduces the laryngeal soft tissue complications encountered in surgery for recurrent respiratory papillomas. Study Design: Retrospective chart review. Methods: Retrospective chart review of all pediatric patients treated for laryngeal recurrent respiratory papillomas between 1984 and 1999 was performed. Thirty-one such patients were identified. Twenty-four were at “high risk” for developing complications based on the number of operating suite visits and the presence of disease at the anterior commissure. Twelve patients underwent 24-hour double pH probe testing. Results: Overall, 13 of 31 patients (42%) developed laryngeal webs. No other soft tissue complications were encountered. Of the patients who had pH probe testing, 12 of 12 (100%) had at least one pharyngeal episode of acid exposure. Of the “high-risk” patients, 10 were treated for reflux and only 2 of 10 (20%) developed webs. Eleven of 14 (79%) of the “high-risk” patients who were not treated for reflux developed webs. The difference in rate of web formation between patients treated for reflux and those not treated for reflux was statistically significant (P = .011). Conclusions: Antireflux treatments for patients undergoing surgery for laryngeal recurrent respiratory papillomas may reduce the soft tissue complications, especially scarring and web formation. Prophylactic antireflux therapy may be warranted in any patient undergoing surgery during which laryngeal mucosal disruption is anticipated. Key Words: Recurrent respiratory papillomas, surgical complications, laryngopharyngeal reflux, laryngeal webs.

INTRODUCTION

Recurrent respiratory papillomatosis (RRP) is the most common benign tumor of the pediatric larynx. Since the 1970s, the surgical treatment of choice has been endoscopic excision, usually performed with a CO2 laser. However, this treatment is only palliative, and patients are often subjected to numerous procedures to keep the airway patent until the disease process regresses and the rate of growth decreases. The complications associated with each procedure can be grouped into those which are immediate (airway fire, hemorrhage, loss of airway, pneumothorax) and those which have delayed onset.

The laryngeal soft tissue complications from surgery for RRP have been described, and include laryngeal webs, stenosis, vocal fold scarring, and arytenoid fixation. Surgical technique itself greatly influences the rate of complications, and the techniques of mucosal preservation, avoidance of bilateral laser treatment at the anterior commissure, and limitation of the depth of thermal injury are generally accepted as necessary to limit complications. However, even the most experienced surgeons encounter soft tissue scarring, especially in patients requiring multiple procedures. A medical therapy that would minimize the conditions that cause or enhance scarring and web formation would be an ideal adjunct to surgical treatment.

There is increasing evidence that laryngopharyngeal reflux (LPR) is a contributing, if not causative, factor in numerous pediatric airway disorders. We have previously presented evidence of reflux in 23 of 30 patients with RRP, 5 of whom were pediatric patients. Laryngopharyngeal reflux has also been implicated in other laryngeal disorders including recurrent laryngeal papillomas, subglottic stenosis, and vocal fold nodules. Laryngopharyngeal reflux has been shown to increase the rate of soft tissue complications in children undergoing surgery for choanal atresia and in children with subglottic stenosis. A relationship between RRP and LPR has been suggested, and it has been postulated that controlling reflux may reduce the papilloma growth rate in a few anecdotal cases. Using 24-hour double pH probe data on several children with RRP, we sought to further investigate a potential relationship between reflux and RRP.
MATERIALS AND METHODS
We performed a retrospective chart review of all patients with RRP who were treated at Brenner Children's Hospital, a tertiary pediatric hospital affiliated with the Wake Forest University School of Medicine (Winston-Salem, NC). Patient records were available dating from 1984 to 1999. Clinical charts and hospital and operating room reports were reviewed. All patients were surgically treated with endoscopic CO2 laser debulking through suspension microscopic direct laryngoscopy. The dates of operating room treatments, frequency of treatments, severity and location of disease, and presence of any soft tissue complications such as scarring, web formation, and stenosis were noted. The presence of a tracheotomy, date placed, and date of decannulation were also documented.

Data were collected on LPR by determining whether the patient had ever been evaluated for reflux with a 24-hour double pH probe (simultaneous distal esophageal and pharyngeal probes) or barium swallow test. The pH probe testing was performed on patients who had laryngeal findings consistent with LPR. The presence and severity of reflux were recorded. Dates of initiation of treatment for reflux were recorded, and the method of treatment was recorded (histamine type 2 [H2]-antagonist, proton pump inhibitor, promotility agents, or Nissen fundoplication). Data were also included concerning pH probe results on medications, as well as follow-up studies to determine the efficacy of Nissen fundoplication.

Patients who had disease routinely treated with the CO2 laser at the anterior commissure or posterior glottic aperture (“posterior commissure”) were deemed to be at “high risk” for developing soft tissue complications. Many of these children had been treated for reflux in some way; therefore, the date of initiation of treatment was correlated with the date of development of soft tissue complications, if any. Patients who developed a complication and were being treated for reflux were grouped together, and those who developed a complication and were not being treated for reflux were grouped together. The number in each group was compared using Fisher’s Exact test. All patients were operated on by residents in the Department of Otolaryngology under direct supervision of a faculty member within the department (J.A.K., G.N.P., or W.F.M.).

RESULTS
Thirty-one patients (14 male and 17 female patients) with laryngeal RRP were treated during the study period. The average age at diagnosis was 2.8 years. Twenty-two patients (71%) were Caucasian, 6 (19%) were black, 2 (6%) were Hispanic, and 1 patient (3%) was Asian American. Collectively, the group required more than 350 operations (mean number, 12 operations per patient). The average interval between surgical treatments was 3.9 months.

Overall, 13 of 31 patients (42%) developed a soft tissue complication, and in the present study the only soft tissue complication encountered was a web. The locations of these webs were found to be as follows: anterior glottic (11), posterior glottic (3), and supraglottic interarytenoid (1). Two patients developed a laryngeal web anteriorly and posteriorly, accounting for 15 webs in all in these 13 patients. The patients with webs generally had more severe disease and, on average, had 18 surgical procedures in all for RRP treatments.

Twelve patients underwent 24-hour double probe pH monitoring, and all 12 (100%) had at least one pharyngeal episode demonstrating LPR. The mean number of pharyngeal episodes was 4.4. Five of 12 (42%) patients had normal esophageal acid exposure, 7 (58%) had abnormal esophageal acid exposure, and 3 (25%) had severe esophageal acid exposure. One patient had LPR witnessed during a barium swallow test, bringing the total number with documented extraesophageal reflux to 13 (42%). All patients with documented reflux were treated. An additional 9 patients (29%) were treated prophylactically without pH probe testing, bringing the total number treated to 22 of 31 (71%). The reflux treatments varied based on severity of LPR disease. The treatments used in the present series were as follows: H2-antagonist and promotility agent (15 [48%]), proton pump inhibitor (6 [19%]), and with Nissen fundoplication, 4 (13%). The patients in the present study who did not receive reflux treatments did not have physical signs or symptoms of reflux.

We retrospectively analyzed patients who had disease that was repeatedly found at the anterior and posterior glottis which required treatment because we think this population is at highest risk for developing a laryngeal web. Twenty-four high-risk patients were identified, and these patients required, on average, 15 surgical treatments each. We specifically studied the date of onset of the laryngeal web and correlated this with initiation of reflux treatment, if any, as well as the method of treatment. Of these 24 high-risk patients, 10 (42%) were treated for reflux and 14 (58%) were not (Table I). The difference in number of operative procedures between the two groups was not statistically significant. In patients treated for reflux, 2 of 10 (20%) developed a laryngeal web and 8 of 10 (80%) did not. In patients not treated for reflux, 11 of 14 (79%) developed a web and 3 of 14 (21%) did not. The rate of laryngeal web formation was compared retrospectively using Fisher’s Exact test, and the difference in web formation between patients treated for reflux and those not treated for reflux was statistically significant (P = .011). Of the two patients who developed webs despite reflux medication, both patients were subsequently proven to have persistent LPR despite medication (two and eight pharyngeal acid exposure episodes, respectively, and both had severe prolonged esophageal acid exposure times) and were treated with Nissen fundoplication. Of the 11 patients who developed webs without reflux treatment, 7 were later found to have reflux, 2 of these 7 patient had severe enough reflux to warrant Nissen fundoplication.

Only one tracheotomy was performed during the course of the present study (1 of 31 [3%]). The patient in

<table>
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<th>Table 1: Reflux Treatment in “High-Risk” RRP Patients.</th>
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<td>No.</td>
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<tr>
<td>Developed laryngeal web (n = 13)</td>
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<td>Did not develop laryngeal web (n = 11)</td>
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Of 24 “high-risk” RRP patients, those who were treated for reflux are compared with those patients who developed soft-tissue complications. The difference in rate of web formation in those treated and those not treated was found to be statistically significant (Fisher’s exact test, P = .011). The difference in mean number of operations between the two groups was not statistically significant.
question had undergone 27 operations and had anterior and posterior commissure involvement. He was evaluated for reflux and was found to have eight pharyngeal acid exposure episodes with severe esophageal acid exposure on a regimen of twice-daily proton pump inhibitors. He underwent Nissen fundoplication, and decannulation was possible 3 months later. He did not develop a laryngeal web. He required only three subsequent operative treatments and has been disease free for 23 months.

DISCUSSION

The delayed complications of surgery for RRP have been reported and include scarring, webbing, and airway stenosis. The only complication encountered in the present study was laryngeal webbing at both the anterior and the posterior commissures. The rate of web formation in previous studies using the CO₂ laser to treat RRP are shown (Table II). Our rate of web formation was 42%, which lies within the reported range of 7% to 47%. The fact that our incidence of web formation tends toward the higher end of this spectrum is attributed to our low threshold of diagnosing any anterior commissure blunting as a web, and to aggressive laser debulking to avoid tracheotomy. We subscribe to the techniques outlined by numerous authors to avoid web formation, which include respecting the anterior commissure, limitation of laser usage at the most anterior portion of each vocal cord, using a low power density, limiting exposure time, and making every effort to preserve mucosa.

Risk factors that may promote development of delayed soft tissue complications are controversial. Wetmore et al.² reported that in patients who had six or more operations, 92% (11 of 12) developed a delayed complication, suggesting that the number of operative procedures is a risk factor. Ossoff et al.⁵ have suggested that the rate of complications is not related to the number of surgical procedures or the interval between those procedures. Our data suggest that the number of procedures does influence the rate of complications because patients who developed a delayed complication had 18 surgical procedures, on average, whereas the average number of surgical procedures for the group as a whole was only 12. Certainly, it would seem that children who have severe RRP requiring frequent laser treatments would be more likely to have a complication than those with minimal disease requiring relatively few treatments. It is in these high-risk patients that efforts to reduce delayed soft tissue complications would be most needed.

There is good reason to suspect that LPR, or extraesophageal reflux, may influence the rate of complications in surgical procedures of the upper airway. Laryngopharyngeal reflux has been shown to complicate conditions such as subglottic stenosis and numerous other pediatric airway disorders such as croup, possibly vocal fold nodules, and possibly sudden infant death syndrome. Laryngopharyngeal reflux also appears to increase the rate of restenosis in children undergoing repair of choanal atresia. These studies support the notion that during surgical procedures involving mucosal disruption, complication rates increase when those traumatized mucosal areas are bathed in acidic solutions that contain pepsin. Control of reflux, indeed, complete suppression of reflux, would seem desirable because it would eliminate the contamination of the surgical site by the highly inflammatory refluxate.

There is still much debate about what is pathological reflux and what is physiological reflux in children and adults. It is known that LPR is distinct and different from gastroesophageal reflux disease, and in our study, slightly less than half (42%) of the patients had normal esophageal exposure despite having abnormal pharyngeal acid exposure. Vandenplas et al.¹⁷ have suggested that the incidence of reflux in the pediatric population is 18%. However, there are few data demonstrating values for physiological reflux and pathological reflux, especially in the pediatric population. Indeed, these values seem to change with age. In our study, all the patients who were treated were older than 1 year of age and were out of the infantile age range. We demonstrated that 12 of 12 patients with RRP (100%) who were tested had evidence of at least one pharyngeal episode during which the pH dropped below 4.0. Whether this represents physiological reflux or ubiquitous pathological reflux is superfluous. The fact that even a single reflux event occurs in these patients is compelling enough reason to treat for total acid suppression. Although not every patient in this group had a follow-up 24-hour pH probe study to document reflux treatment efficacy, many children had persistent reflux even on a regimen of twice-daily proton pump inhibitors, and four patients required Nissen fundoplication.

We realize that the present retrospective study has limitations and is an uncontrolled study. The surgeons involved in the present study were not blinded to reflux treat-
ment at the time of web diagnosis, although every effort was made to be impartial. We sought to identify any bias in the study in several ways. We sought to determine whether the complications were encountered by any one particular surgeon, and they were not. In fact, all operations were performed by residents with direct faculty supervision. We studied the mean number of procedures for the group treated for reflux and for the group not treated for reflux, and the mean number of procedures was not significantly different for these two groups. Although the patients who were evaluated and treated for reflux represent our more recent patients, we do not think this represents a significant bias between the two treatment groups because the mean number of surgical procedures was statistically the same. It is true that not all patients were evaluated for reflux, and 24-hour pH probe–proven control of reflux was not carried out in every patient. However, because 4 of 12 patients tested had reflux refractory to medical management, pH probe drug efficacy studies should be considered, particularly in high-risk patients and in patients who have developed soft tissue complications.

There has been previous work demonstrating a potential relationship between LPR and RRP. Borkowski et al. have reported three anecdotal cases in which children with severe RRP had gastroesophageal reflux disease (GERD) or LPR diagnosed with 24-hour pH probe testing. After treatment for GERD, all three patients required less frequent operative treatments to control the papilloma growth. This raises the following intriguing question: Does treatment for reflux decrease the rate of papillomatous growth in children with RRP? The present study provides no data to answer this question because the frequency of operative intervention is somewhat subjective and is based on patient symptomatology and the surgeon’s expectation of voice and airway. Retrospective analysis of the effect of acid suppression on the severity of RRP can be anecdotal at best. However, anecdotal evidence can be compelling: The one patient in the present series who required a tracheotomy for extremely aggressive RRP was found to have severe reflux on a regimen of proton pump inhibitor taken twice a day. Decannulation was possible in this patient three months after Nissen fundoplication (7 mo after undergoing the tracheotomy). He required medical management, pH probe drug efficacy studies should be considered, particularly in high-risk patients and in patients who have developed soft tissue complications. Although the patients who were evaluated and treated for reflux represent our more recent patients, we do not think this represents a significant bias between the two treatment groups because the mean number of surgical procedures was statistically the same. It is true that not all patients were evaluated for reflux, and 24-hour pH probe–proven control of reflux was not carried out in every patient. However, because 4 of 12 patients tested had reflux refractory to medical management, pH probe drug efficacy studies should be considered, particularly in high-risk patients and in patients who have developed soft tissue complications.

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Given the evidence that LPR can increase surgical complications, we are currently treating every pediatric patient who undergoes a surgical procedure wherein laryngeal mucosal incisions are performed with acid suppressive medication. This practice is not based on cost analysis of treating complications versus cost of medical therapy, nor is it based on double-blinded, randomly controlled studies that have documented its necessity. Studies such as these do not exist yet. However, because of the multiple reflux–inducing risk factors that airway surgery portends to patients, as well as the “ubiquitous” finding of pharyngeal acid exposure events in patients with airway disease, we think that acid suppression is beneficial. In patients who develop complications or in patients who have persistent evidence of LPR, 24-hour double pH probe studies for drug efficacy are warranted, as well as escalation of therapy carried out based on results of testing and clinical outcome.

CONCLUSION

The incidence of delayed soft tissue complications from surgical treatments for RRP was reduced in our patients who were treated for LPR. In the patients who were tested, 100% had evidence of pharyngeal reflux to a pH value less than 4. Evaluation of patients with RRP for reflux by means of 24-hour double pH probe is warranted, and confirmation of reflux control by repeat pH testing on a medication regimen is recommended. Further prospective studies of the role reflux plays in RRP and other surgically treated pediatric airway disorders are planned.

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