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# Managing Juvenile Recurrent Respiratory Papillomatosis and Care of the Voice

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## INTRODUCTION

Juvenile recurrent respiratory papillomatosis (JRRP) is a rare disease characterized by wartlike growths (Fig 15–1) in the aerodigestive tract with potentially devastating consequences despite its benign histopathology. As the larynx is the most common site of disease involvement, the implications for vocal function and voice abnormalities are readily apparent. In addition, repetitive surgical management to remove JRRP can predispose to well-intentioned but overzealous management with potential long-term impact on vocal fold function. Even with advances in the tools used to manage this disease there is great risk of chronic and irreversible change to the voice. Fortunately, greater understanding of the pathophysiology, natural history, and evolving treatments of JRRP now affords the luxury of prioritizing voice in the management of this recalcitrant disease.

### Epidemiology

JRRP is defined as disease onset prior to age 12 and is the most common benign neoplasm of the larynx in the pediatric population. The incidence is estimated at 4.3 per 100,000 children,[1] with 75% being diagnosed by their fifth birthday[2] and boys and girls affected essentially equally.[3] However, our experience is that JRRP is not uncommonly diagnosed in the first year of life and there can be a delay as long as one year from onset of the predominant symptom of hoarseness to ultimate diagnosis. In one study, 75% of affected children were the firstborn, vaginally delivered infants of primigravid, teenage women of low socioeconomic

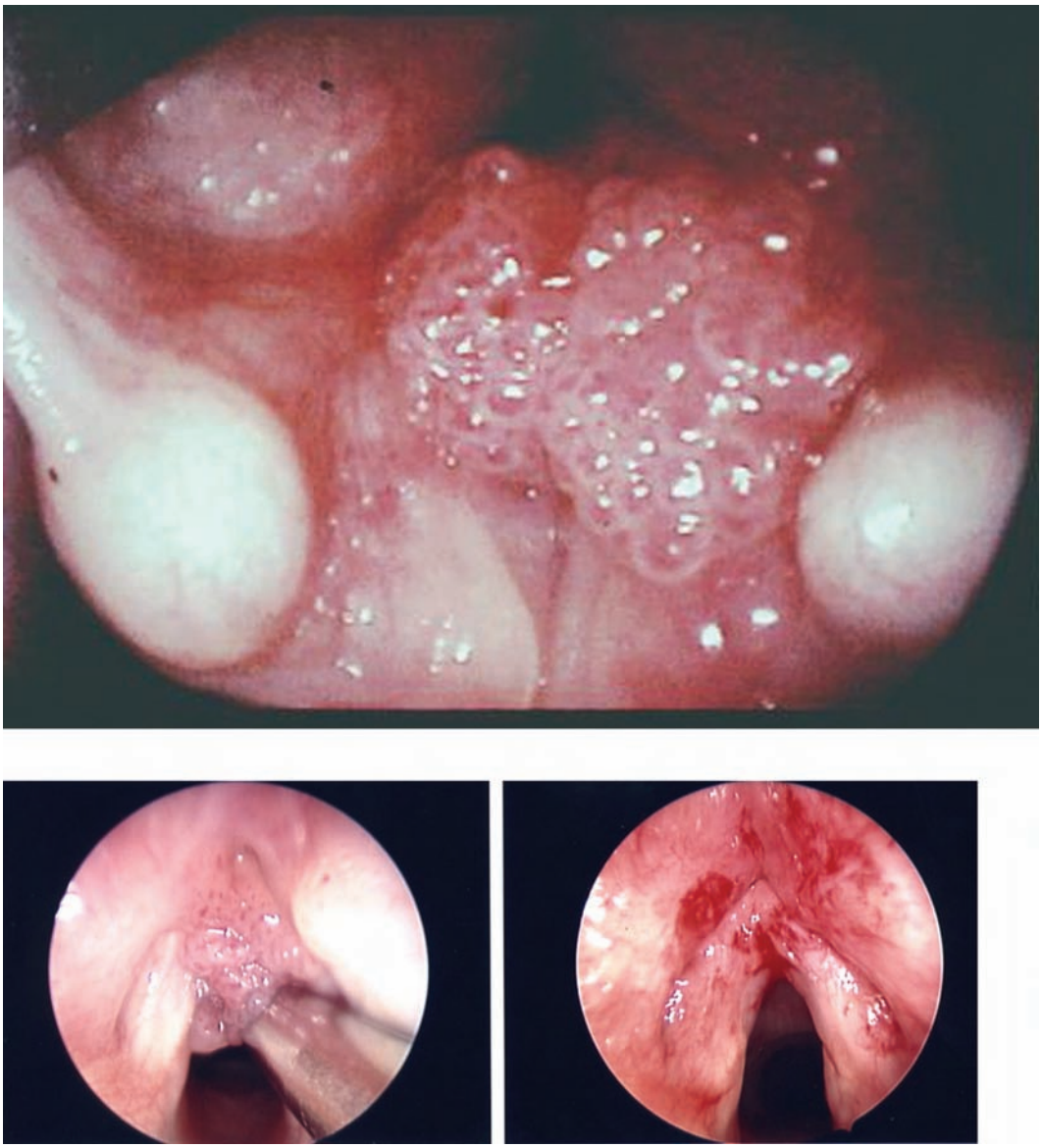


**Fig 15–1.** The classic appearance of pedunculated, exophytic, "cauliflowerlike" papillomas with diffuse laryngeal involvement.

status.[4] Diagnosis at a younger age corresponds to greater severity of disease, more frequent surgical intervention, and greater risk of progressive disease.[5,6]

The disease is caused by human papillomavirus (HPV), and vertical transmission from mothers with genital condylomata to newborns is generally accepted. In one series, 7 of every 1000 births to women with genital warts resulted in newborns with JRRP, corresponding to an odds ratio of 231 compared to vaginal deliveries from

unaffected women.[7] However, the incidence of JRRP in offspring of women with genital condylomata is still surprisingly small, estimated at 1 in 400 delivered vaginally from a mother with a history of disease in the genital tract.[8] In addition, cesarean section is not necessarily protective and not currently recommended by the American College of Obstetrics and Gynecology as an elective option to prevent disease.

The recurrent nature of the disease subjects the patient to repetitive surgeries with a high cumulative cost. In a review of a national registry of children with RRP, patients underwent more than 19 lifetime procedures, averaging more than 4 per year.[9] More than 15,000 procedures are performed annually in the United States on children with JRRP at an estimated cost of over $150 million.[1] The estimated lifetime cost to treat one case ranges from $60,000 to $470,000.[10]

## Pathophysiology

Nearly all cases of JRRP are caused by HPV types 6 and 11, the same types found in genital condylomata. Isolation of other HPV types within JRRP is extremely rare, and the rare involvement with types 16 and 18 is associated with a risk of malignant transformation. HPV type 11 is associated with a more aggressive disease course and greater likelihood of distal airway spread compared with type 6.[11] The presence of viral particles or DNA within the aerodigestive tract is not sufficient for infection or subsequent development of papillomas. HPV can lie dormant within otherwise healthy mucosa, and is replicated along with host cells. The exact mechanism which results in active infection and papilloma growth is still unknown, although key viral coded proteins are known to bind to and inhibit the tumor suppressing gene products p53 and pRB within the host cell.[12] Local immune dysfunction has been considered as a component to the development of disease in JRRP.

Papillomas typically occur in regions where ciliated and squamous epithelium are juxtaposed, and readily form in similar interfaces from iatrogenic causes such as a tracheostomy.[13] The most common regions affected by RRP are the upper and lower ventricle margins, the undersurface of the vocal folds, the laryngeal surface of the epiglottis, the carina, and bronchial spurs, the nasal limen vestibule, and the nasopharyngeal surface of the soft palate.[4] Injury to adjacent normal tissue from surgical intervention or extraesophageal reflux can lead to proliferation of disease. Tracheotomy patients tend to have earlier presentation and more widespread disease, and the procedure itself may hasten spread distally into the trachea and pulmonary parenchyma.[14]

## Clinical Presentation and Evaluation

Symptoms of varying degrees of respiratory obstruction are the most common presentation of JRRP. Hoarseness is most often the chief complaint, and, as noted above, delay in diagnosis from the onset of symptoms of greater than a year is not atypical. For this reason, children can also present with stridor or respiratory distress at the time of initial diagnosis. Patients are often treated for croup, asthma, allergies, or vocal nodules in the interim. At times the definitive diagnosis is made because of the development of significant stridor. Rarely, a patient will present with failure to thrive, recurrent pneumonias, or an acute life-threatening airway event.

A thorough history of a child with hoarseness is critical to establish the diagnosis of JRRP from other causes. The nature

and timing of the symptoms, prior airway trauma or intubation, congenital anomalies, significant comorbidities, and associated symptoms must be addressed. Maternal history of vaginal or cervical condylomata should be assessed and follow-up recommended. A slowly progressive inspiratory or biphasic stridor is suggestive of a glottic or subglottic lesion that requires visualization.

A complete physical examination with visualization of the pharynx and larynx is typically sufficient to make a definitive diagnosis. In the stable patient without acute airway compromise, flexible nasolaryngoscopy is performed on the awake patient to assess anatomy, presence of lesions, and laryngeal function. Patients presenting with tachypnea, cervical hyperextension, air hunger, hypoxia, or other signs of acute respiratory compromise may require evaluation in the operating room by direct laryngoscopy with endotracheal intubation if necessary.

Prior to or at the time of initial surgical treatment, direct laryngoscopy is performed in the operating room under general anesthesia. Photo or video documentation of disease extent is very helpful if not essential to monitor effectively the subsequent response to therapy and to communicate findings with parents. A staging system developed by Derkay and Coltrera is in common use to allow reliable communication of findings between providers.[15]

## TREATMENT OF RECURRENT RESPIRATORY PAPILLOMATOSIS

No predictive medical or surgical cure exists for JRRP, and surgical debulking of disease is the mainstay of treatment to control symptoms ranging from hoarseness to life-threatening airway compromise. The goals of any particular intervention will vary with the disease status of the patient, although there are common themes. Securing a safe airway by decreasing critical tumor burden is always of paramount importance. However, improving voice quality likely prompts the most visits to the operating room overall and is used as a guide to intervene before significant airway obstruction occurs. Accomplishing these two goals is ideally done in a manner that preserves underlying normal structures, increases the time between interventions, avoids the need for tracheotomy, and reduces the likelihood of morbidity and complications. A biopsy for HPV typing should be performed at the initial surgery for prognostic purposes, and typically it is not necessary to repeat this at subsequent excisions unless clinical indicated or to look for changes brought about by therapeutic intervention.

It is critical to recognize that surgical treatment itself becomes an integral part of the disease process. This is currently unavoidable for several reasons. First, it is not possible to determine an effective margin of disease because healthy cells can still contain latent virus that will become active in the future. Second, trauma to adjacent healthy tissue at the time of surgery can lead to spread of disease. Third, the disease is recurrent and typically requires multiple procedures over the lifetime of the patient. Finally, overly aggressive excision of papilloma can result in scar and web formation with significant consequences for voice. Therefore, with repetitive interventions as the mainstay of management, there is likely to be some negative impact on the laryngeal structures. Although essentially unavoidable, it is still necessary to maintain constant awareness of this unique interaction to improve outcomes, particularly in regard to voice.

Adjuvant treatments to surgery are expanding and show promise in lengthening the interval between surgical interventions and possibly decreasing the time to disease remission. Given the risks of general anesthesia and the potential complications of repetitive surgery, these agents can result in substantial improvements in quality of life for patients. Voice is now a critically recognized entity in the overall management of patients with JRRP. Medicines and techniques that help preserve normal laryngeal anatomy and physiology represent major advances in treatment.

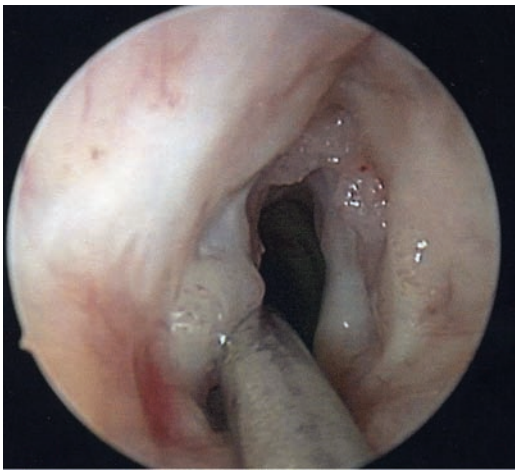


**Fig 15–2.** Microdebrider removal of exophytic, pedunculated papilloma.

## Surgical Treatment

Surgical tools for excision of recurrent respiratory papillomas are microlaryngoscopic cold steel instruments, the microdebrider, or various lasers. Cold steel excision, once the only option, is still utilized for removal of disease, predominantly in the adult form of RRP, which tends to be less aggressive and recurrent compared to JRRP.[16] Until recently, the $CO_2$ laser was the favored method of treatment in the pediatric population.[12] Currently, the microdebrider is the preferred instrument for the surgical management of JRRP, especially when the disease is pedunculated and exophytic (Fig 15–2).[17] Ultimately, the disease status and anatomy of the patient determine the most effective intervention at the time of surgery.

Effective communication and cooperation with the anesthesiologist prior to and during surgery on RRP is critical. The bulk and location of disease along with the desired treatment modality will determine the appropriate method of ventilation. Pediatric anesthesiologists have become increasingly familiar with and comfortable with maintaining the airway using spontaneous ventilation and adjuvant anesthetic agents. This provides the best view of the larynx and extent of disease and the best access for removal. Endotracheal intubation may be required initially for excessive disease and at times jet ventilation or apneic techniques are employed.

### *Microdebrider*

The microdebrider is a powered instrument with oscillating blades and suction that is compatible with most of the goals of surgical treatment of JRRP. The device allows very precise removal of tumor with fine control of depth of excision and no surrounding thermal damage. It eliminates the other inherent risks and costs of laser use including fire, longer surgical times, release of HPV DNA into the air, distal airway damage, and scar formation. A randomized prospective trial comparing the $CO_2$ laser and microdebrider found the use of the latter was associated with more rapid voice improvement, decreased cost, and shorter operative time.[18] Others have found similar benefits for reduced time, cost, and surrounding

tissue damage.[19,20] The microdebrider is still limited in very fine or sessile disease and papilloma that involve the anterior commissure or ventricles and maintains the potential for surrounding tissue mechanical trauma. Knowledge of the blade sizes and cutting surfaces as well as the recommended speed of the oscillating debrider blade are essential in reducing iatrogenic damage from the microdebrider.

### $CO_2$ Laser

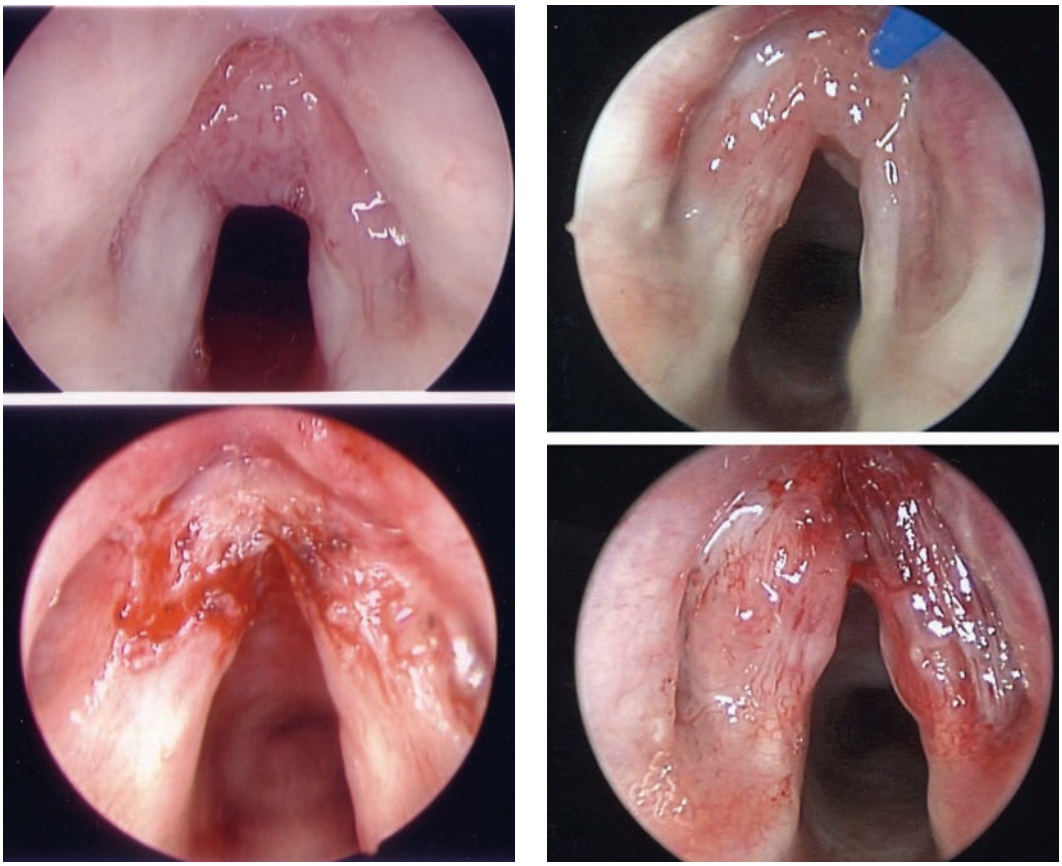
The $CO_2$ laser was the mainstay for treatment of JRRP for decades. Its effective wavelength is absorbed by water in tissues, and combined with the operative microscope results in precise vaporization of papilloma. The technique is bloodless, and advances in the technology reduced surrounding tissue damage. However, $CO_2$ laser treatment is limited to line of sight disease, is costly, and carries significant risks. (At present the line of sight difficulty may be obviated by the newly developed flexible $CO_2$ laser.) The risk of airway fire requires a laser safe endotracheal tube. HPV DNA may be released in the plume, placing operating room personnel at risk.[21] In addition, the development of anterior and posterior glottic scars and webs was reported in several series, with rates as high as 36%.[19] Part of this may be due to surrounding thermal injury from the laser. Therefore, this technique may place voice preservation at risk.

### Angiolytic Lasers: Pulsed Dye Laser, Pulsed KTP Laser

The 585-nm pulsed dye laser and 532-nm pulsed KTP laser overcome many of the limitations of the $CO_2$ laser. These wavelengths are absorbed by oxyhemoglobin, resulting in subepithelial microvascular damage and involution with relative sparing of the epithelium. Therefore, bilateral glottic lesions can be treated in the anterior commissure without subsequent web formation as has been demonstrated in practice (Fig 15–3).[22] The fibers can be passed through a flexible scope, suction device, rigid bronchoscope side port, or adaptor and can be used in adults in a clinic setting under local anesthesia. With a 2-mm depth of penetration, it is well suited for smaller, sessile lesions, but it is not effective for large exophytic papillomas. From a voice preservation perspective, this laser treatment holds promise in the treatment of lesions in the anterior commissure and ventricle as well as the free edge of the vocal folds and infraglottic region and has already demonstrated improved voice satisfaction in patients after treatment.[23,24] However, as compared to the microdebrider, there is a longer period of voice recovery with hoarseness persisting for 5 to 7 days after treatment.

## Adjuvant Therapies

In a query of American Society of Pediatric Otolaryngology members, adjuvant treatments were required in 20% of JRRP patients.[17] Typical criteria include greater than 4 surgeries per year, rapid return of aggressive disease, and distal airway spread.[14] The rarity of the disease is a significant challenge to well-controlled, randomized, prospective trials on the effectiveness of these treatments. The majority of evidence available consists of case series using various antiviral therapies. Due to the lack of adequate controls, it is difficult to judge if these therapies are altering a disease process that inherently demonstrates wide variability both within and between patients in terms of natural history. However, in those



A B

**Fig 15–3. A.** Anterior commissure involvement of RRP with significant impact on voice. Removal using the pulsed dye laser. **B.** Pulsed dye laser removing anterior commissure disease extending onto right true vocal fold.

patients with aggressive disease requiring surgery as often as every 6 weeks, adjuvant therapy that reduces tumor burden will likely reduce frequency of intervention and likely reduce long-term voice changes.

### *Interferon α-2a*

Interferon α is produced naturally by infected leukocytes and exerts antiviral activity via activation of proteins that interfere with various stages of the virus life cycle. Systemic administration to JRRP patients demonstrated significant effectiveness in multi-institutional, randomized trials.[25] However, it is associated with significant side effects including an influenzalike illness, neuropsychiatric complications, neutropenia, and thrombocytopenia. In addition, prolonged therapy lasting up to several years is necessary and a rebound phenomenon is observed in up to one-third of patients with initial clinical response following cessation of therapy.[25]

### Cidofovir

Intralesional injection of cidofovir has received a great deal of attention over the past decade as an adjuvant treatment for JRRP. It is approved by the Food and Drug Administration for the systemic treatment of cytomegalovirus retinitis in HIV patients, and the mechanism for activity against HPV is not clearly established. Several uncontrolled case series have demonstrated effectiveness of cidofovir in concentrations of 5 to 10 mg/mL,[25] including a series of severely affected children with a mean follow-up of 51.6 months.[26] Systemic administration is associated with potential nephrotoxicity, hepatotoxicity, and neutropenia. Concern also exists about both vocal fold thickening from the injection and possible carcinogenic effects of local administration. However, local injection is not associated with significant systemic concentrations and animal studies failed to demonstrate significant scarring or tumorigenicity at concentrations used in humans.[27]

Despite numerous anecdotal reports of cidofovir effectiveness, the overall risks and benefits are difficult to establish given the lack of large, well-controlled studies. The mechanism of action, definitive toxicity profile, and optimum treatment dose and timing are undefined. Despite these limitations, the cumulative evidence does suggest that cidofovir is a relatively safe and useful adjunct in the treatment of aggressive or poorly controlled JRRP refractory to standard therapy. Benefits include increasing surgical interval, improving quality of life, decreasing the chance for iatrogenic damage to the larynx, and potentially hastening remission.

### Indole-3-Carbinol

Indole-3-carbinol is a nutrient naturally found in cruciferous vegetables and is a nutritional supplement approved by the Food and Drug Administration. It affects estrogen metabolism to favor the production of 2-hydroxyestrone over 16α-hydroxyestrone, with a proposed effect of decreasing the risk of hormone-dependent tumors, including RRP.[28] It is a systemic therapy without significant side effects, although long-term use has been associated with bone density concerns. It has been reported to be effective in treating adult onset RRP in various case series.[25] It does not appear to be as useful in children and no large, prospective, well-controlled study has been published to date to verify the benefits of indole-3-carbinol.

### Immune Modulation

The most beneficial form of therapy is, of course, prevention. At present there is now an FDA-approved quadrivant vaccine (Gardasil-Merck) indicated for the prevention of disease caused by human papillomavirus (HPV) types 6, 11, 16, and 18. A second, bivalent vaccine (Cervarix-GSK) is on the horizon. From the point of view of management of JRRP the quadrivalent vaccine, which includes types 6, and 11 would be preferred over a vaccine that did not cover these HPV types.

Results of the phase 3 study on the highly effective quadrivalent vaccine against human papillomavirus types 6, 11, 16, and 18 were recently published.[29] The trial was targeted at women for the prevention of anogenital disease. Given the high prevalence of genital HPV in the population at large and the risk of JRRP from vertical transmission, it seems reasonable that widespread vaccination could significantly impact the incidence of JRRP. This will likely take many years to become apparent. Gardasil has been approved for use in girls and women 9 to 26 years of age; it is currently recommended

in the vaccine schedule published by the American Academy of Pediatrics and consists of three injections spaced over 6 months.

A targeted vaccine for treatment of HPV-related disease is under development. Heat-shock protein E7 (HspE7) is a recombinant fusion protein consisting of heat-shock protein Hsp65 of *Mycobacterium bovis* BCG and the E7 protein from HPV type 16. An open-label trial on children with JRRP was conducted using three subcutaneous injections over 8 weeks that demonstrated significant increases in intersurgical interval with only mild to moderate injection-site reactions.[31] Further studies are pending.

### *Management of Extraesophageal Reflux Disease*

Extraesophageal reflux has been suggested to exacerbate RRP. In a retrospective review of children undergoing multiple surgical procedures, those treated with antireflux regimens developed laryngeal webs significantly less often compared with those not treated.[32] The authors recommended prophylactic antireflux regimens for patients undergoing procedures that disrupt the laryngeal mucosa to prevent soft-tissue complications.

## JUVENILE RECURRENT RESPIRATORY PAPILLOMATOSIS AND THE VOICE

The recurrent nature of this disease and its propensity for laryngeal involvement make voice complaints a universal feature and concern both during and after treatment. It is remarkable that many patients who have undergone upward of 60 to 80 procedures maintain as good a voice as they do. Papillomas of the anterior commissure and inferior aspect of the vocal folds can be extremely difficult to access and safely manage surgically. Even when these lesions are accessible, overly aggressive excision can lead to soft tissue complications such as scars and webs leading to voice deficits. Regardless of the particular surgical technique used, the underlying disease process remains the same. Until a cure is discovered or vaccination becomes universal, surgery will remain a necessary tool to manage symptoms until disease remission. Although slow regression tends to occur at the onset of puberty,[33] the cumulative result of the disease and treatment over time can lead to lifelong poor voice quality.

## The Rady Children's Hospital Experience

Our experience with JRRP is extensive with more than 20 active patients in varying stages of disease and management at any time. At the initial procedure, suspension microlaryngoscopy using spontaneous ventilation (Parsons or Benjamin laryngoscope, Karl Storz Endoscopy-America Inc, Culver City, Calif) and bronchoscopy is performed, extent of disease documented with photographs before and after surgical manipulation (photographs are taken at each procedure permitting rapid comparison of disease state throughout the treatment period), biopsy with HPV typing is sent, and debulking of gross, bulky disease carried out using a powered laryngeal microdebrider (Xomed, Jacksonville, Fla). Disease in the anterior commissure region is not manipulated at all. Disease is staged according to the system established by Derkay and Coltrera.[15] No perioperative steroids are administered and patients are discharged home on the same day.

Follow-up endoscopy is scheduled 4 to 6 weeks later in an effort to assess rapidity and location of regrowth. At this junction multiple modalities of treatment are readied, including the microdebrider and the 585-nm pulsed dye laser (PDL). Preoperative discussion with the family reviews the issues of airway management and voice management and use of the PDL for sensitive areas, such as the anterior commissure, difficult to reach areas such as the ventricles and infraglottic regions, and for finer, sessile lesions. Bulky disease is removed with the microdebrider. If the PDL is used the family is told to expect some degree of increased hoarseness for approximately 5 to 7 days, after which they can anticipate overall improvement in the voice. Follow-up endoscopies are scheduled based on the age of the patient, the extent of papilloma regrowth, concerns for airway obstruction, and the status of the voice.

A comprehensive discussion of all available adjuvant therapies is held with the parents of those patients with severe disease. In our institution, severe disease is defined as patients requiring surgery every 8 weeks or less to maintain a patent airway. First-line adjuvant therapy is intralesional cidofovir at a concentration of 5 mg/mL. The family is made aware that there will be 4 or 5 injections carried out at two 3-week intervals and then the need for continued injections is reassessed (Fig 15–4). Injec-

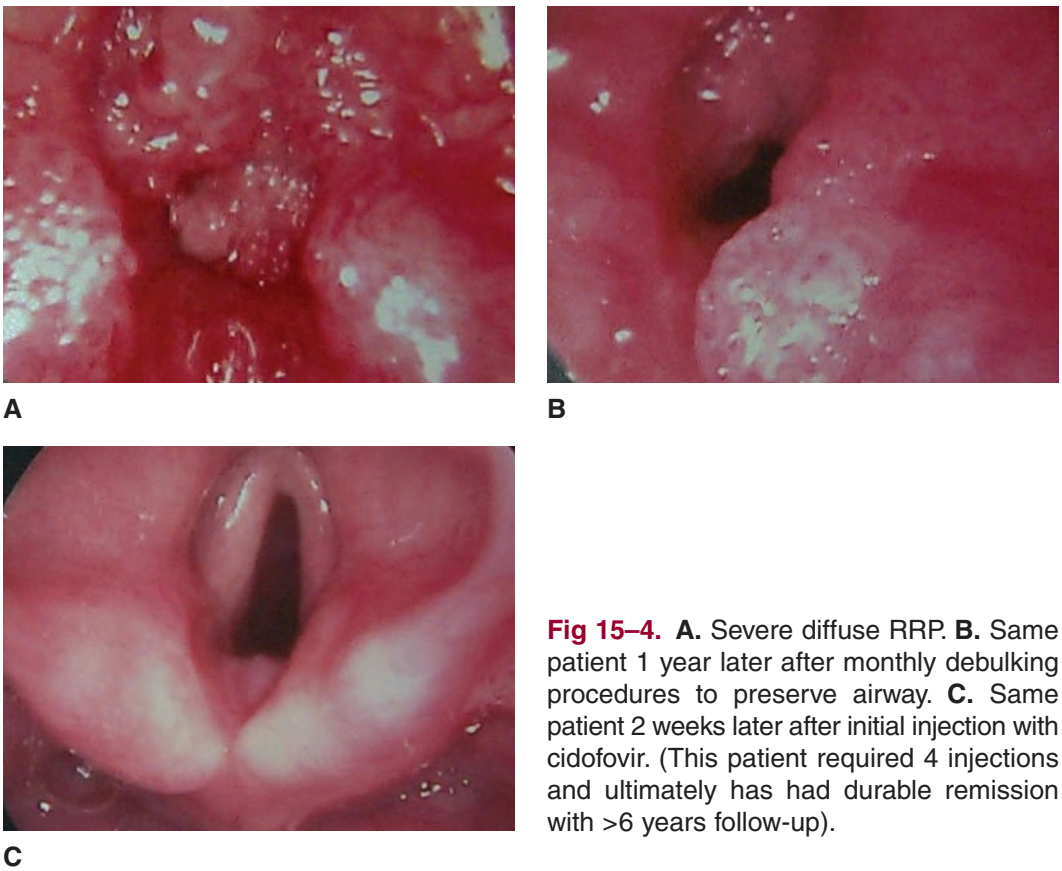



**Fig 15–4.** **A.** Severe diffuse RRP. **B.** Same patient 1 year later after monthly debulking procedures to preserve airway. **C.** Same patient 2 weeks later after initial injection with cidofovir. (This patient required 4 injections and ultimately has had durable remission with >6 years follow-up).

tions are performed with either a straight laryngeal needle (Leurlock, Straight 8598B, Karl Storz Endoscopy-America Inc, Culver City, Calif) or with a gastrointestinal sclerosing needle (Bard, Billerica, Mass) passed through the side port of a pediatric bronchoscope in the setting of difficult to reach lesions. For laryngeal disease usually 1 to 1.5 mL is injected into the various sites of involvement, including the anterior commissure region. The injection is done at the base of the lesion after debridement or laser of the overt disease. A small wheal is raised at the sites of injection with great care taken not to compromise the airway. Patients are monitored with monthly complete blood counts, chemistry panels, and liver function tests for potential toxicities and repeat biopsies are sent every other treatment session. We have now injected approximately 20 children with cidofovir and have seen complete and durable remission in almost 60% of cases and significant improvement in disease in another 20%. Ultimate voice results have been very good, although there is often some degree of mild persistent raspiness. There are patients who do not seem to respond to cidofovir, especially when they present with extensive prior surgical manipulation and scarring of the laryngeal tissues. We have not encountered any significant adverse effects from the cidofovir. Although there may be some thickening of the laryngeal mucosa with the cidofovir, this is difficult to distinguish from the thickening that occurs with other surgical manipulation of the larynx.

As mentioned above, there is some evidence that extraesophageal reflux disease can exacerbate RRP. Consequently, whenever there is extensive disease in the larynx, spread of disease beyond the larynx, or if the child is receiving cidofovir injections, GERD management is instituted with either an H2 blocker or a proton-pump inhibitor, along with dietary and positional manipulation. At times an esophagogastroduodenoscopy with biopsy is carried out by our pediatric GI colleagues to look for spread of disease into the esophagus, overt evidence of GERD, and for evidence of coexistent disease such as *H. pylori* or eosinophilic esophagitis.

The patient with scar or web formation in the setting of active JRRP presents a challenge. Whenever possible, treatment of these soft-tissue complications is delayed until a clinically significant level of remission of papillomas is achieved. At that time, they are treated the same as in a patient without JRRP. However, an important consideration is that a web may hide papilloma that does not resolve until it is uncovered and treated directly.

## Layers of Expertise

In addition to the pathophysiology and treatment modalities used, there are many factors that likely contribute to voice outcomes in JRRP. Although these potential pitfalls are unavoidable in some circumstances, and certainly not ameliorated by the rarity of the disease, they must still be taken into account when considering voice outcomes. The treatment setting provides the foundation for multiple layers of expertise necessary to successfully manage this disease. A dedicated children's hospital with subspecialty departments covering a wide referral base is most likely to encounter enough patients with JRRP to gain facility in treating it. Outcomes in such a setting reflect the cumulative experience of the surgeon and anesthesiologist whose effective cooperation is so critical. Understanding the need for a "shared airway" and having expertise in spontaneous ventilation is typically required for optimal management. In

addition, awareness of "cutting edge" therapies, and access to, and experience with different surgical tools and adjuvant therapies that increase surgical intervals and limit soft-tissue complications may be more readily available at an institution that treats a high volume of JRRP patients. As pediatricians become more aware of JRRP and refer voice abnormalities earlier, younger patients with smaller airways will be referred making all of the above issues even more important. In addition, continuing research into the various modalities often used in adult laryngeal disease, such as the ongoing studies by the editor (C.J.H.) and the author (M.B.P.) on angiolytic laser treatment, are critical.

## Speech Therapy

At what point does speech therapy play a therapeutic role in the child with JRRP? Now that greater attention is given to functional outcomes of treatment, this question becomes increasingly important. A series of 4 prepubescent children with at least 12 months of remission from JRRP reported normal voice satisfaction on the voice-related quality of life questionnaire that was not significantly different from controls.[34] However, objective analysis of these patients in the same study showed more hoarseness, lower average fundamental frequency, and a higher relative average perturbation. Although a very small study, the results reflect what seems obvious to those who care for these patients. Voice quality is clearly affected during active disease and beyond remission even if it is not considered significant by the young patient. The appropriate timing and effectiveness of speech therapy for these children remains to be determined. We have begun to involve our speech therapists in management of the chronic hoarseness issues with these patients once the need for aggressive and repetitive surgical intervention has diminished. However, our results with speech therapy are too preliminary to make any recommendations for when these patients should be referred and for how long therapy should be continued.

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# 19

# Paradoxical Vocal Fold Motion

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## INTRODUCTION

Diagnosis and treatment of paradoxical vocal fold motion (PVFM) are challenging for the otolaryngologist and especially for the pediatric otolaryngologist. Commonly referred to as vocal cord dysfunction (VCD), PFVM is now the preferred term for the affliction. PVFM involves episodic, inappropriate adduction of the vocal folds during the inspiratory phase of the respiratory cycle resulting in intermittent (usually partial) glottic obstruction. It is important to distinguish between those patients with a true laryngeal disorder and those with other conditions that may appear to cause similar symptoms. In order to determine the etiology of this complex disorder, comprehensive neurolaryngologic evaluation, usually including dynamic laryngeal assessment, strobovideolaryngoscopy, and laryngeal electromyography (LEMG), is essential. Consultation with a neurologist, pulmonologist, and gastroenterologist are required often. Psychological and voice therapy evaluations have proven useful, as well.

## OVERVIEW

PVFM is a diagnosis that has been used widely, but the patients receiving this diagnosis may actually be suffering from one or more of a variety of disorders that may appear to impair upper respiratory tract function. Moreover, many patients who have paradoxical vocal fold adduction have been diagnosed incorrectly as having asthma. Originally described by Patterson et al[1] in 1974 as Munchausen's stridor, the etiology was first thought to be psychogenic. Other causes and exacerbating factors have been identified since that time, as well as other disorders that may present with similar symptoms. Maschka et al[2] described a classification scheme for paradoxical vocal fold motion based on seven categories (Table 19–1), providing useful descriptions of the presenting symptoms associated with each of these diagnoses.

In addition to psychogenic causes and those listed in Table 19–1, other common diagnoses in patients referred to laryngologists for suspected PVFM include respiratory

**Table 19–1.** Maschka et al Classification Scheme for Paradoxical Vocal Fold Motion

| Feature | History | Associated Signs and Symptoms |
|---|---|---|
| Brainstem compression | Often otherwise unremarkable | Vagal dysfunction (velopharyngeal insufficiency, GERD) |
| Severe cortical injury | Static encephalopathy or cerebrovascular accident | Sialorrhea, upper airway obstruction, poor neuromuscular control |
| Nuclear or lower motor neuron injury | Medullary infarction, amyotrophic lateral sclerosis, myasthenia gravis | Other neurologic signs related to underlying etiology |
| Movement disorders | Exacerbated by stress or exertion | Other focal dystonias, tremors, rigidity, bradykinesia, decreased reflexes |
| Gastroesophageal reflux* | Otherwise unremarkable | May occur during calm, crying, or feeding |
| Factitious symptoms or malingering | Conscious effort to deceive | Underlying secondary gain |
| Somatiziation/conversion disorder | Unconscious manifestation of stress | Well-motivated, high achievers |

*= Reflux is associated more commonly with laryngospasm than with true paradoxical adduction, in our experience (VD, MJH, RTS), and usually is accompanied by symptoms and signs of laryngopharyngeal reflux (LPR).

dystonia, laryngospasm, increased laryngeal irritability (usually due to reflux), and supraglottic collapse. All of these conditions are seen fairly commonly in children and adults; but in our experience, treatable organic etiologies are much more prevalent than psychogenic or serious neurologic causes.

## Neurologic

Respiratory dystonia is a particularly important cause of PVFM. The condition is related to spasmodic dysphonia, but it affects respiration rather than voice. Dystonias that affect the respiratory function of the larynx may be accompanied primarily by other dystonic movements such as blepharospasm, mandibular dystonia, torticollis, spasmodic dysphonia, or upper-extremity tremors. This type of PVFM typically is better with sleep and worsens with stress and exertion. However, usually dystonic PVFM occurs alone and is called respiratory dystonia.[3,4] Patients with rhythmic adduction and abduction of the vocal folds may be found to have an associated palatal myoclonus. Kelman and Leopold[5] reported a patient with a brainstem lesion abnormality causing PVFM and suggested that the proximity of adductor and abductor neurons to each other in the nucleus ambiguus may permit inappropriate stimulation from the respiratory centers. The series reported by Maschka et al[4] also documented two patients with known central neurologic eti-

ologies for their laryngeal movement disorders that were characterized by stridor and paradoxical vocal fold adduction during inspiration; but the patients had normal phonation.

Respiratory dystonia should be differentiated from psychogenic stridor and reflux-induced laryngeal spasm. Patients with true respiratory dystonia tend to demonstrate fairly consistent patterns of paradoxical vocal fold movement (adduction during inspiration) during respiratory and speech tasks, although the severity may vary. Many patients have worsening of their symptoms during stress and exertion. They differ from patients with reflux-induced laryngospasm who usually have acute episodes of sudden airway obstruction due to forceful vocal fold adduction, rather than chronic adduction associated with inspiration. They also differ often from patients with psychogenic causes in their consistency even when they are not being observed.

In children and adults, intracranial etiologies also must be investigated. Several intracranial abnormalities have been reported to give rise to PVFM, including Arnold-Chiari malformation, cerebral aqueductal stenosis, and compression of the nucleus ambiguus.[4] We have seen it associated with multiple sclerosis as well. Static encephalopathy also may be associated with PVFM and may be accompanied by global developmental delay, hypertonia, spastic diplegia, and sialorrhea. These patients typically present as older children or adolescents, whereas those suffering from brainstem compression present typically during infancy or early childhood. The diagnosis in patients with cerebral compromise may be complicated by a narrowed airway at the level of the nasopharynx or oropharynx which causes increased inspiratory pressures and, therefore, may mimic PFVM or actually cause paradoxical adduction through the Bernoulli effect. Correction of the upper airway obstruction may result in improvement at the level of the glottis in some cases.

## Psychiatric

Patients may suffer episodes of airway obstruction in response to emotional stress or anxiety; and any past psychiatric history should be noted. "Munchausen's stridor," Patterson et al's[1] original description of unclassified stridor, has been supported by multiple other reports.[4,6–7] It is likely that some of those reports inadvertently included patients with organic disorders such as respiratory dystonia that have been recognized much more recently. Vocal fold dysfunction of psychiatric origin has been called by many other names in the past including psychogenic stridor, functional stridor, and functional upper airway obstruction. It is imperative that the clinician rule out organic causes of airway obstruction and vocal fold dysfunction before attributing the respiratory symptoms to a nonorganic cause. Psychogenic PVFM is most common in young women and in members of the health care profession.[7] Over half of patients meet the diagnostic criteria for a psychological disorder, and up to 18% have a history of prior factitious disorder.[6,7] Other disorders such as anxiety, depression, personality disorders, stress disorders, or a history of sexual abuse may be present. Many of these patients have a characteristic worsening of symptoms on observation and abatement of symptoms when they believe that they are not being observed. The main difference between a factitious/malingering disorder and a conversion disorder is that factitious/malingering disorders

are expressed for secondary gain. According to the DSM-IV-TR,[8] a factitious disorder requires the presence of (1) intentional production or feigning of physical or psychological signs or symptoms, (2) motivation for the behavior is to assume the sick role, and (3) absence of external incentives for the behavior (eg, economic gain, avoiding legal responsibility, improving physical well-being, as in malingering). Malingering is not considered a medical condition and is described as the intentional production of false or exaggerated symptoms motivated by external incentives, such as obtaining compensation or drugs. Patients with conversion disorder typically have a preceding psychological or emotional incident that may have triggered an episode, although expert psychotherapy may be needed to identify the incident. Unlike malingering patients, those suffering from a conversion disorder are not aware that any underlying psychological insult is associated with their complaints. They are typically well motivated and compliant with therapy. Extensive testing in patients with conversion disorder typically yields no organic origin. Altman et al[9] documented a psychiatric illness in 70% of their patients presenting with PVFM, and other case reports have supported this observation.[6,7] This lends support to the original supposition that psychogenic or "conversion" disorder is present in some patients. However, it is not clear immediately in many cases whether there is a causal relationship between psychiatric abnormalities and PVFM, and thorough evaluation for psychiatric and organic causes is required in all cases.

## Increased Laryngeal Irritability

Recent upper respiratory tract infection (URI) may have preceded the onset of symptoms and been associated with increased airway irritability that may lead to PVFM, especially if laryngopharyngeal reflux (LPR) is also present. Laryngeal hyperreactivity may be induced by LPR even without an URI, and the clinician should inquire about symptoms of laryngopharyngeal reflux including cough, throat clearing, hoarseness, globus sensation, "postnasal drip," and excess mucus production. LPR is a known cause of laryngeal irritability and has been reported in some studies to be present in up to 80% of patients with PVFM.[7,10]

The increased laryngeal irritability caused by LPR contributes to the laryngeal hypersensitivity seen in some patients with PVFM or laryngospasm mistaken for PVFM. Treatment of LPR must be accompanied by treatment of any other concomitant disorders. Several inhaled antigens have been shown to increase laryngeal irritability and may trigger PVFM. Previously described triggers include air pollutants (dust, smoke), perfumed products (perfume, soap, detergents, and deodorants), chemical agents (paint), animal fur, and pollen.[10] Any relation between symptoms, environment, and potential exposure should be investigated. An associated history of irritant exposure may be present as may a history of food or environmental allergies. A full allergy workup is warranted in patients in whom inhaled irritants are a suspected trigger. Caution must be exercised in associating PVFM with multiple chemical sensitivity disorder because of the controversies and complexities surrounding this diagnosis.

## Supraglottic Collapse and Vocal Fold Hypomobility

Cystic fibrosis, partial airway obstruction, and other conditions that require high inspiratory pressures may draw the vocal folds or

the supraglottic tissues toward the midline into the airway, through the Bernoulli effect.[11] Careful observation should be made to see if supraglottic collapse is resulting in obstruction of airflow. This may be caused by conditions in which the laryngeal skeleton or tracheobronchial tree is weakened, such as tracheomalacia or laryngomalacia. However, supraglottic (aryepiglottic fold and false vocal fold) collapse also may occur in children with tissue redundancy or laxity in the absence of any other abnormality. In addition, bilateral vocal fold paralysis commonly results in vocal fold adduction on inspiration. The narrow glottis causes high airflow, which in turn draws the vocal folds to the midline during inspiration (Bernoulli effect). Conditions such as cricoarytenoid joint dysfunction causing vocal fold hypomobility may present with stridor that can be confused with PFVM as well. However, the symptoms usually are less dramatic in these patients because they have innervated vocal folds with muscle tone that helps resist the Bernoulli effect. So, passive paradoxical adduction of the vocal folds usually is not seen in patients with normally innervated vocal folds.

## EVALUATION

### History and Physical Examination

Specific areas of questioning are necessary when working up a patient with suspected PVFM. Patients are seen commonly for otolaryngologic evaluation after they have been treated for refractory asthma unresponsive to bronchodilator or steroid therapy, or after an episode of acute respiratory distress. The patients have a history of emergency room visits for dyspnea treated with intubation and occasionally even tracheotomy. In children, the episodes of respiratory distress often are associated with strenuous exercise, prompting an evaluation for asthma. However, unless asthma is present concurrently, methacholine challenge test may have been negative, but occasionally may be falsely positive for asthma (as discussed below). PVFM presents commonly in children during high levels of exertion, particularly in high-performance athletes. This may have very severe ramifications. For example, patients may be striving to achieve an athletic scholarship and require evaluation for safety of continued participation in sports. Failure to achieve an accurate diagnosis and effective treatment may be life altering. Initially, symptoms typically are present during exertion or stress. However, as the condition progresses, symptoms may be present even at rest. PVFM episodes may be associated with stridor interpreted as wheezing, suprasternal retractions, dysphonia, or aphonia. The dysphonia or aphonia may precede the acute episode and linger after its resolution. Exercise-induced reflux may cause intermittent laryngospasm that can be mistaken for PVFM during the eliciting athletic activity as well. If this condition is suspected, athletic activity should be performed with a multichannel pH-impedance monitor in place to confirm the diagnosis. Due to the demand of their schedules, many school athletes are prone to eating habits which may promote LPR, including eating late at night or immediately prior to an athletic event.[12,13]

A full allergic history should be taken including any respiratory inhalant allergens that have an association with the patient's dyspnea. The physician should inquire about recent respiratory infections as they may cause increased laryngeal irritability. A focused psychiatric history should be obtained with any positive answers pursued

with a potential referral to a psychiatrist. Specific questions should be asked regarding stress levels and any correlation of social stress or other psychological factors with onset of respiratory symptoms. A history of throat clearing, globus sensation, excessive mucus, and hoarseness may indicate LPR as a potential etiology. Additional historical aspects of each topic are discussed with various specific etiologies.

Physical examination is the gold standard for diagnosing PVFM. A full head and neck examination should be performed including testing of the functions of all cranial nerves. Dynamic endoscopic laryngeal examination should note signs of reflux including posterior pachydermia, arytenoid erythema and edema, subglottic fullness, and vocal fold edema. Vocal fold motion should be documented and signs of upper aerodigestive tract collapse noted. Strobovideolaryngoscopy should be included even in patients who are not hoarse because the traumatic vocal fold contact that occurs during PVFM, laryngospasm, and other respiratory obstructive events results in vocal fold injury in many patients.

The presence of PVFM is confirmed through observation of vocal fold adduction during the inspiratory phase of respiration. Typically the anterior two-thirds of the vocal folds medialize leaving a diamond-shaped posterior glottic chink, although near-complete glottic closure occurs in some patients. Observation of supraglottic or other structural collapse associated with symptoms also establishes a diagnosis. Although observation of active vocal fold adduction on inspiration confirms the diagnosis (Video 19–1), the office examination may be normal if the patient is not placed in a situation that elicits the respiratory distress. Therefore, for patients who complain of airway distress during exercise, facilities should be present to allow the patient to perform physical activity with intensity equal to the eliciting activity. Cardiac and respiratory monitoring may be beneficial, although not necessary in all patients. This will allow for evaluation of any concomitant cardiac arrhythmias that may be present. There are case reports of patients who develop ventricular tachycardia during exertion which presents as airway obstruction (personal communication, Michael Johns, MD, 2007). In this situation, inspiration against glottic adduction allows a decrease in intrathoracic pressure which increases venous return in order to maintain cardiac output. Other maneuvers, such as repetitive rapid deep inspirations, alternating phonating the /i/ vowel and sniffing, and other speaking tasks may elicit the abnormal laryngeal movement in some patients.[5]

LEMG provides information regarding neuromuscular function which can be used to determine whether adductor muscles are active during the inspiratory phase of the respiratory cycle. EMG gives information regarding the amount of muscle contraction and synchrony of paired firing. In patients with a spasmodic dysphonia, a condition related to respiratory dystonia, EMG demonstrates an increase in discharge from the vocalis muscle at rest and during phonation as well. Warnes and Allen[14] utilized EMG to determine the effectiveness of biofeedback and voice therapy. They showed that during a course of treatment, electrical discharge from the laryngeal musculature at rest decreased until a normative level was reached. This was achieved with surface electrodes which significantly increases feasibility over needle electrodes when treating children. To the best of our knowledge, similar therapy has not been tried for respiratory dystonia, but the concept seems worthy of investigation.

Airway fluoroscopy also may be used in diagnostic evaluation to determine the

presence of diaphragmatic dys-synergism with the vocal folds. This results in an uncoordinated depression of the diaphragm while the vocal folds are still in the midline.

Flow-volume spirometry is very useful in supporting the diagnosis of PVFM, too. During an acute episode, "flattening" of the inspiratory limb is seen, demonstrating an extrathoracic upper airway obstruction (Fig 19–1). When the patients are asymptomatic, the flow-volume loop will return to normal. The expiratory/inspiratory flow ratio is typically greater than 2.[15] Unlike asthma and other forms of intrathoracic small airway obstruction in which $FEV_1$ is reduced, the $FEV_1$ is preserved in PVFM. Pulmonary function testing also may be used in association with methacholine challenge or bronchodilator medication to rule out concomitant asthma. Guss and Mirza[15] published a report of seven patients sent to an otolaryngology clinic for choking and dyspnea. Only three patients in the study were found to have a 20% reduction in their $FEV_1$ consistent with the presence of asthma. Three of the other patients developed documented PVFM with methacholine challenge typically utilized for diagnosis of asthma. This is most likely due to excessive laryngeal hypersensitivity, although the mechanism has not been proven. These patients may be misdiagnosed with asthma and found to be nonresponsive to treatment. Although these patients were not the same ones diagnosed with PVFM, Newman et al[7] found that 53 of 95 patients with confirmed PVFM suffered from asthma as well. Table 19–2 compares the various features of PVFM versus asthma.[12]

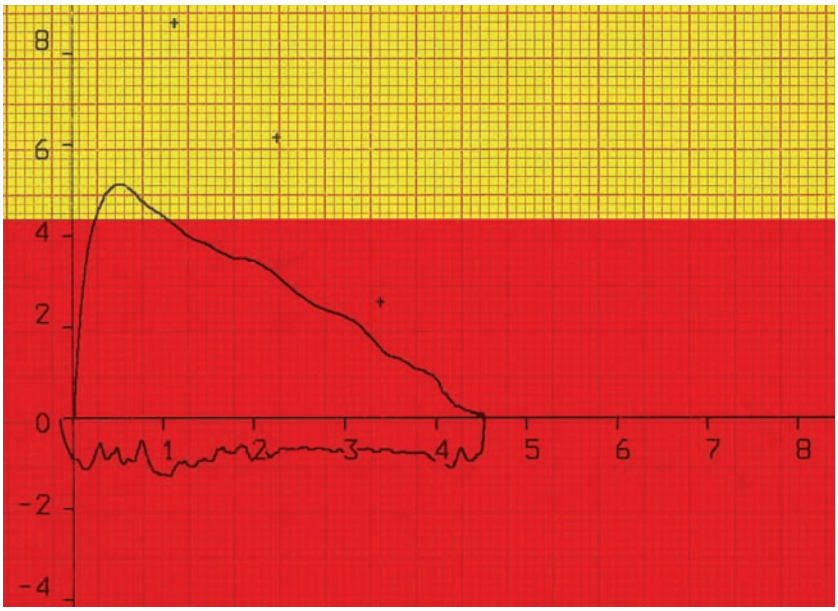


**Fig 19–1.** The flow-volume loop above demonstrates flattening of the inspiratory limb, demonstrating an extrathoracic airway obstruction as seen in PVFM.

**Table 19–2.** Distinguishing Diagnostic Features of PVFM and Asthma[12]

| Diagnostic Feature | PVFM | Asthma |
|---|---|---|
| Chest tightness | Yes/No | Yes |
| Throat tightness | Yes | No |
| Stridor with inhalation | Yes | No |
| Wheezing with expiration | No | Yes |
| Types of triggers | Exercise, extreme temperature (hot or cold), airway irritants (GERD), emotional stressors | Exercise, extreme temperature (hot or cold), airway irritants, allergens, emotional stressors |
| Number of triggers | Usually one | Usually multiple |
| Usual onset of symptoms after beginning exercise | <5 min; however, can be variable | >5–10 min |
| Recovery period | 5–10 min | 15–60 min |
| Response to bronchodilators and/or systemic corticosteroids | No response | Good response |
| Nocturnal awakening with symptoms | Rarely | Almost always |
| Female preponderance | Yes | No |

## TREATMENT

Patients who present to the emergency room with an acute episode of respiratory distress typically are treated as a patient suffering from an asthma attack or an acute airway obstruction. Many patients receive beta-2 agonists and corticosteroids. If the symptoms do not abate, intubation, and at times emergency tracheotomy, is used to control the airway. Heliox, a combination of helium and oxygen, which has a lower molecular weight and is less dense than oxygen, can ease the dyspnea of patients with respiratory distress.[16] The lighter molecular weight gas results in less turbulence across the narrowed glottis. Christopher et al[17] found that the wheezing and dyspnea resolved in all patients suffering from laryngospasm when a 20% helium/oxygen mixture was administered. However, these emergency treatments usually are used in patients in whom the diagnosis of PVFM has not been made or even suspected.

There are many different treatment approaches for the treatment of PVFM, and the most appropriate modalities depend upon the cause. Biofeedback is an effective method for retraining some patients to manage an acute episode. Laryngeal image biofeedback, initially described by Bastian and Nagorsky[18], has been shown to be an effective learning tool for patients to mimic target tasks. This study demonstrated that patients can reliably alter laryngeal movements

and postures using laryngeal image feedback in the absence of auditory-perceptual cues. Visual laryngoscopic biofeedback in association with speech therapy has been effective as definitive treatment in some patients, although it is only partially effective in most. A variety of other noninvasive therapeutic approaches have been used with varying success including respiratory retraining, psychological educational approaches, and other techniques to restore sensory and motor function and control. Behavioral management may be partially effective in some cases. For example, many patients have less prominent paradoxical adduction during nasal breathing than during oral breathing, especially patients who do not have respiratory dystonia. Focusing on nasal breathing is very helpful for such patients in managing a crisis situation. Martin et al[19] described a speech therapy program which divided treatment of the acute episode into seven steps. These steps were designed around the concepts of pitch change, diaphragmatic breathing, and extrinsic muscle tension reduction. A summary of the seven steps is included in Table 19–3.

When patients have a psychiatric component to their respiratory distress, it is

**Table 19–3.** Seven-Step Behavioral Treatment for PVFM[19]

| |
|---|
| 1. Providing the patients slow direction and acknowledging the patients' fear and helplessness and that the stridor is real |
| 2. Utilizing a behavioral approach to exercises, so that with self-awareness and good breathing patterns, the patients will be prepared to voluntarily control an attack when it occurs. |
| 3. Advising use of diaphragmatic breathing, such as is used by professional singers, directs attention away from the larynx. This gives the patients a place to focus body awareness, so respiratory effort can be utilized without producing laryngeal, clavicular, or thoracic tension. The patient concentrates on pushing the lower abdomen out with inspiratory descent of the diaphragm. On expiration, the patient concentrates on utilizing support from the lower abdominal muscles. |
| 4. Advising use of "wide-open throat" breath, concentrating on having the lips closed, the tongue lying flat on the floor of the mouth behind the lower front teeth, with the buccal areas of the mouth relaxed, releasing the jaw gently, and using diaphragmatic inhalation and exhalation techniques. |
| 5. Advising the patient to focus on exhalation interrupts the patients' tendency to feel that they are unable to get any more breath and to hold onto their breath. They are taught to exhale, release their breath, and then allow inhalation to follow effortlessly. They are allowed to develop an exhalation count, so they know they can maintain exhalation up to that number of counts, and avoid gasping for air. |
| 6. Increasing self-awareness of the breathing sequence of inhalation and exhalation decreases the feeling of helplessness via increased self-awareness of the correct sequence of the breathing process. |
| 7. Interrupting effortful breathing is fostered by developing the attitude that their breathing does not have to be actively performed but is part of a natural body process that can be gradually trusted and practiced. |

often helpful not to imply initially that they have a psychiatric illness which is causing their problem. First, the psychological symptoms may be secondary. Second, even if they are not, many patients and families are more willing to accept psychological consultation if it develops as an outgrowth of good rapport with a laryngologist and voice pathologist. If patients are told abruptly that their illness is psychiatric in origin, they may be resistant to voice therapy and psychotherapy. In addition, the diagnosis may prove to be wrong. Although both speech-language pathologists and psychologists have a role in behavioral treatment of PVFM, a speech-language pathologist is more appropriately suited for initial treatment. In addition to addressing the emotional issues associated with this illness, speech-language pathologists are instrumental in teaching the patient how to avoid and/or deal with an acute episode of dyspnea. Initial referral to a psychologist may imply to the patient and family members that the physician believes the problem to be "in the patient's head." The anxiety associated with PVFM and related disorders is a significant component of the disorder. The need for psychologic evaluation and treatment for both the patient and the family is a concept that should be introduced gradually to ensure that the patient is openly receptive to the treatment.

Botulinum toxin has been used with success to treat respiratory dystonia. This concept was introduced in 1992 by Brin et al.[3] In their series of 7 patients with PVFM, 4 were offered vocalis muscle Botox injections with outstanding relief of laryngeal symptoms. Five of the 10 patients reported by Altman et al[9] responded at least partially to botulinum toxin injected into the thyroarytenoid muscle, and two of them had other dystonias. In our experience, EMG-confirmed adductor muscle activity during respiration, in combination with other findings that suggest respiratory dystonia, indicates that Botox has a higher likelihood of being an effective treatment. Interestingly, respiratory dystonia which is not accompanied by dysphonia responds extremely well to low doses of botulinum toxin injected into the thyroarytenoid muscle, although associated respiratory dysrhythmia may persist.

More aggressive airway management strategies have been described. Lloyd and Jones[20] have described a patient in whom an arytenoidectomy and partial cordectomy were performed. PVFM persisted 2 weeks after the procedure, and the patient then underwent a stitch lateralization of the vocal fold. The percutaneous stitch was removed after 6 weeks and the patient was symptom free for 1 year. Eventually, she did require tracheotomy and completion arytenoidectomy. This treatment, although seemingly aggressive, may be necessary to decannulate patients who have refractory PVFM, but such intervention should be needed in exceedingly rare cases (none, in our experience).

Soft-tissue surgery has proven very helpful in patients with supraglottic collapse. Excision of redundant supraglottic tissue (usually using a $CO_2$ laser) eliminates the collapsing tissue and alters aerodynamics resulting in cure of the symptoms in most cases.

## CONCLUSION

PVFM is uncommon but not rare. Dystonic and psychogenic causes are encountered frequently and can be treated effectively. Supraglottic tissue collapse, reflux, other causes of laryngeal hyperirritability, and other conditions that may produce PVFM must be differentiated from true paradoxic

adduction. Organic etiologies should be sought in all patients. Botulinum toxin provides effective control for patients with respiratory dystonia, and voice therapy and psychological intervention are valuable in many cases. Surgery is necessary only rarely for PVFM, but is curative in most patients with isolated supraglottic collapse. Otolaryngologists should be able to diagnose and treat effectively virtually all patients who present with symptoms consistent with PVFM in collaboration with an expert team of therapists and consulting physicians in other specialties.

## VIDEOS ASSOCIATED WITH THIS CHAPTER

**Video 19–1.** Video of example of PVFM seen on videolaryngoscopy and demonstration of relief with biofeedback exercises.

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