

Vocal Cord Dysfunction and Asthma

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Opinion Statement

Vocal cord dysfunction (VCD) is a functional disorder of the vocal cords characterized by exaggerated adduction of vocal cords during inspiration and/or expiration causing respiratory and laryngeal symptoms. VCD can exist in isolation and coexist with asthma, or it can mimic asthma. The missteps during the VCD and asthma diagnostic process and subsequent faulty clinical conclusions can lead to mistreatment and increased health care utilization that can last for years. Therefore, diagnostic precision in conjunction with optimal therapeutics is a prerequisite for the best patient outcomes in this patient population. An integrated approach is frequently required using multiple diagnostic modalities to make a correct diagnosis. The treatment options, usually applied in a step-wise progression, depend on the severity of presentation and the underlying type of VCD. Future studies should address the better identification of specific phenotypes of VCD and their corresponding treatments.

Introduction

Vocal cord dysfunction (VCD) is a functional disorder of the vocal cords characterized by exaggerated adduction of vocal cords during inspiration and/or expiration causing respiratory and laryngeal symptoms. As a clinical entity, VCD was first introduced in 1983 by Christopher et al. who reported five patients with VCD that mimicked attacks of asthma [1]. However, this syndrome had

initially been described by Dunglinson in 1842 [2] and subsequently by MacKenzie in 1869 who first observed abnormal vocal cord motion [3]. In the last several decades, more than a dozen different diagnostic terms have been used to describe VCD patients [4••]. The current nomenclature consists of the following terminology: VCD, which is used mostly among allergists and

pulmonologists, paradoxical vocal fold motion disorder (PVFMD), which is used primarily among otolaryngologists, and inducible laryngeal obstruction (ILO), which has been recently adopted but has not yet gained wide acceptance [5].

The etiology of VCD has not been clearly elucidated, and various mechanisms have been proposed including exaggerated protective laryngeal reflex with altered autonomic balance and laryngeal hyperresponsiveness [6, 7]. VCD is exacerbated/induced by inhalant triggers, occurs more often in females, and is associated with medical and psychological comorbidities [8•, 9, 10]. Three distinct clinical phenotypes of VCD have been described: irritant (spontaneous), exertional, and psychological [11–13]. There is a significant overlap in clinical symptoms/triggers between these phenotypes, and the existence of a separate psychological phenotype has been questioned [14]. Additionally, our group has identified three subtypes of VCD where one type of VCD exists in isolation, the second type mimics asthma, and the third type coexists with asthma [8•, 15].

The relationship between asthma and VCD is of particular interest for allergists and pulmonologists because these are the “refractory to treatment” patients most often seen in their specialty clinics. While asthma is defined by bronchial hyperresponsiveness and bronchial constriction, VCD is characterized by laryngeal hyperresponsiveness and laryngeal constriction. Therefore, one can think of VCD as “asthma of the upper airway.” Furthermore, VCD has been recognized for its ability to cause asthma-like symptoms resulting in erroneous diagnosis of asthma [8•, 16••]. Our group has showed that 42.4% of all VCD subjects were previously misdiagnosed as having asthma for an average of 9.0 years [8•]. Therefore, the timely diagnosis of VCD

is critical in reducing morbidity, health care utilization, and cost associated with this condition [15]. Notwithstanding similarities in clinical presentation, there are important differences between VCD and asthma including certain clinical symptoms, lack of response to asthma treatments, and absence of “larynx remodeling” in VCD patients. Furthermore, ours and other groups have reported that VCD coexists with asthma in up to one third of patients which makes the diagnosis and management of VCD even more complex [8•, 16••, 17]. The clinical relevance of VCD and asthma coexistence is unknown. For example, expiratory closing of vocal cords has been reported in asthmatics, which in some may reflect a normal physiologic response, while in others, this may represent an abnormal finding [18, 19]. Finally, it is noteworthy that there is an emerging concept of a significant overlap between VCD, chronic cough, muscle tension dysphonia, and globus sensation and these conditions are considered to be the part of the continuous spectrum in terms of pathophysiology and treatment [20•, 21, 22•].

The proposed diagnostic criteria for VCD include appropriate clinical symptoms, laryngoscopic evidence of significant vocal cord adduction, and optional confirmatory pulmonary function test (PFT) findings such as flow-volume loop changes and absence of bronchial hyperresponsiveness [4••]. However, these criteria are fraught with diagnostic challenges due to inadequate sensitivity and specificity and possible overlap with asthma or other laryngeal disorders. In this review article, we aim to outline the state-of-the-art approaches in diagnosis and treatment of VCD and discuss important diagnostic and therapeutic pearls and pitfalls in the management of this complex condition.

Diagnosis

As highlighted previously, VCD is a disorder that can exist in isolation or coexist with asthma. VCD itself can also mimic asthma, making the diagnosis even more difficult. It is the authors’ experience that up to a third of VCD patients have coexisting asthma. [8•]. The lack of VCD awareness among many practitioners as well as patients often contributes to a delay in making a VCD diagnosis. Frequently, many patients are diagnosed with asthma based on history alone and without objective testing. Furthermore, the investigative tools at our disposal are often handicapped by inherent deficiencies in their ability to accurately pinpoint the diagnosis. Therefore, the path to the diagnosis of VCD

vs. asthma or both can be very challenging and requires combining various approaches in order to properly treat these patients. For example, in our retrospective study, 50% of patients had a chest CT scan performed unnecessarily as part of evaluation of their VCD symptoms. The missteps during the VCD and asthma diagnostic process and subsequent faulty clinical conclusions can lead to mistreatment and increased health care utilization that can last for years [8•, 15].

Though the exact prevalence of VCD is unknown, we feel that it is important to be aware of prominent clinical associations. We know that VCD occurs more frequently in women and the presence of psychological disease and GERD is more frequent compared to asthma [8•]. We have also identified several novel comorbidities, including irritable bowel syndrome and chronic pain in association with VCD [8•]. Therefore, the presence of these associated conditions may increase a clinical suspicion for VCD. On the other hand, although post nasal drainage can be a trigger for VCD, the presence of allergic rhinitis is not different between those with VCD vs. asthma [8•]. Additionally, a sudden onset of symptoms after an inhalation exposure to a trigger may increase the suspicion for VCD [10].

There are several features in the clinical presentation that might suggest the presence of VCD. The common respiratory symptoms seen in the majority of VCD patients include dyspnea, cough, and chest tightness [8•, 16••, 23]. However, these symptoms are also common in asthma and therefore do not distinguish asthma from VCD. Our group has developed an easy-to-use four-question screening questionnaire, the Pittsburgh VCD Index, which is very sensitive and specific in distinguishing VCD from asthma patients [24••] (Table 1). The Pittsburgh VCD Index consists of four questions that identify VCD patients: the presence of dysphonia and throat tightness, a sensitivity to odors, and absence of wheezing. At the cutoff of four points, the Pittsburgh VCD Index has a sensitivity of 83%, specificity of 95%, positive predictive value of 96%, and negative predictive value of 77%. It should be noted that although wheezing was present in close to 40% of VCD patients, it was more frequently present in asthmatic patients. Therefore, the presence of wheezing does not rule out VCD if patients have a positive response to other questions. Pinto et al. developed a VCD screening checklist to help identify the presence of VCD in those with severe asthma and found that an affirmative answer to 4 out of 6 items suggested the presence of VCD [25]. These authors noted that cervical wheezing was present in 93% of their cohort with VCD and severe asthma. Our group and others have not found this to be the case [23, 24••, 26]. Another group developed a ten-question Dyspnea Index, with ratings from 0 to 4 for

Table 1. Pittsburgh Vocal Cord Dysfunction Index

Pittsburgh VCD Index (positive if score $\geq$ 4 points)	Points
Do you experience throat tightness during your respiratory flare-ups?	Yes—4 points
Do you experience dysphonia (change in your voice) during your respiratory flare-ups?	Yes—2 points
Are your respiratory symptoms triggered by any odors (smells)?	Yes—3 points
Do you experience wheezing during your respiratory flare-ups?	No—2 points

each question, and a score higher than 10 considered abnormal. The study did not specifically look at the presence of VCD, but instead aimed to determine if the symptoms were originating from the upper airway, which would include VCD. A diagnosis of asthma would have to be considered separately [27]. Vertigan et al. developed the Newcastle Laryngeal Hypersensitivity Questionnaire as a non-invasive tool to measure laryngeal paresthesia in patients with various laryngeal conditions such as chronic cough, VCD, muscle tension dysphonia, and globus sensation. This 14-item questionnaire could differentiate patients from healthy controls, though each item requires the participant to rate their answer on a scale of 1 to 7. The effect of the presence of asthma on the results of this questionnaire is also unknown [28]. Ye et al. developed a 15-factor one-item questionnaire that had a sensitivity of 89% and specificity of 73% for diagnosing asthma versus VCD. The scoring for this questionnaire is less than ideal to calculate, which may limit its utility in clinical practice [29].

Several different testing methods in evaluating VCD have been suggested. The gold standard for diagnosis is considered to be laryngoscopy, with direct visualization of abnormal vocal cord motion, either at rest, with phonation, or with provocation with known triggers, including irritants or exercise. Classic laryngoscopic findings consistent with VCD include inspiratory vocal cord adduction of the anterior two thirds with a posterior diamond-shaped chink. Additionally, in those patients without complete vocal cord closure, greater than 50% closure of the vocal cords during inspiration and/or expiration has been suggested as a confirmatory finding for VCD [4••]. Some patients will develop dynamic closure of the airway at the supraglottic level and will have a very similar clinical presentation to the classic VCD patients. If a specific irritant or olfactory odor is suggested by the patient to be a trigger and resting laryngoscopy is normal, it is often useful to waft that trigger under the patient's nose during the procedure as it often induces abnormal motion of the vocal cords, confirming the VCD diagnosis. For symptoms with exercise, we routinely perform serial spirometry in addition to laryngoscopy after an exercise challenge test to rule out exercise-induced bronchospasm along with VCD. Unfortunately, the greatest difficulty in performing exercise challenge is that it does not always mimic the "real-world" conditions and one cannot always induce the symptoms. In some patients, the continuous laryngoscopy exercise test may be superior to a regular exercise challenge followed by laryngoscopy due to its ability to detect short-lived abnormal vocal cord movements in real time [30, 31•].

Several issues have been identified with using laryngoscopy for diagnosing VCD. Morris et al. have reviewed VCD literature and reported that inspiratory adduction of vocal cords was seen in 32% and expiratory adduction in 9% of 1587 VCD patients [4••]. Therefore, the laryngoscopic exam is frequently normal in VCD patients, especially if they are asymptomatic or their symptoms cannot be provoked. Some researchers have recommended using videography in those patients where the friends or family members can record the patient with a video camera during their symptomatic phase [32]. One study has reported chronic low-grade abnormal movement of vocal cords during the asymptomatic phase which cannot be seen with regular flexible laryngoscopy [33]. Furthermore, interobserver variability can lend itself to subjectivity in making the diagnosis of VCD. For example, a previous laryngoscopy study demonstrated slight to moderate agreement beyond chance in diagnosing vocal

cord changes seen in laryngopharyngeal reflux (LPR) among different examiners [34•]. Haines et al. have tried to standardize VCD laryngoscopic exam findings and found moderate interrater agreement. They did conclude that despite the interrater disagreement, their VCD laryngoscopic appearance scale still yielded a positive VCD diagnosis [35]. It is noteworthy that despite the limited sensitivity of laryngoscopy in diagnosing VCD, a normal laryngoscopic exam excludes other causes of upper airway obstruction that should be considered in the differential diagnosis of VCD such as subglottic stenosis, vocal cord paralysis or paresis, or neurologic disorders.

For those practitioners who do not perform laryngoscopy, less invasive diagnostic tools such as spirometry have been utilized in diagnosing VCD. Spirometric features that suggest the diagnosis of VCD include flattening of the inspiratory flow-volume loop and FEF-50/FIF-50 (ratio of forced flow at 50% of expiration to forced flow at 50% of inspiration) >1.0 – 2.0 [10]. In some patients with expiratory VCD, obstructive changes on the expiratory flow-volume loop can be seen. Persistent flattening of the inspiratory and expiratory flow-volume loops suggests a fixed cause of upper airway obstruction and requires further workup. In the literature, the frequency of inspiratory flow-volume loop flattening in VCD patients ranges from 23 to 46% [4••, 36]. While others have found differences in the FEF-50/FIF-50 ratio [37], Murry et al. found no difference between VCD subjects and controls [38]. Therefore, the absence of spirometric abnormalities suggesting upper airway obstruction does not exclude the diagnosis of VCD. Additionally, changes in inspiratory flow-volume loop do not indicate that the patient has VCD because these can be seen in normal subjects, other causes of upper airway obstruction, or sleep apnea patients [39, 40].

Given the overlap in symptoms between VCD and asthma, it is sometimes necessary to perform bronchoprovocation testing with methacholine in order to definitively rule out an asthma diagnosis. While a negative test is useful in ruling out asthma, methacholine itself has been demonstrated to trigger VCD leading to a false-positive methacholine challenge and misdiagnosis of asthma [41, 42]. It has been our experience that methacholine challenge test is more likely to be positive due to asthma if there is a disproportionate decrease in FEV₁ (forced expiratory volume in the first second) with concomitant decrease in FEV₁/FVC (forced vital capacity) ratio, the presence of a concave expiratory flow-volume loop, and a normal appearing inspiratory flow-volume loop. Alternatively, in a false-positive methacholine challenge due to VCD, there is a proportionate decrease in FVC and FEV₁ without significant change in FEV₁/FVC ratio and a flattening of the inspiratory flow-volume loop. Additionally, one can perform laryngoscopy to confirm vocal cord adduction triggered by methacholine [11]. Finally, an exhaled nitric oxide test may hold promise as an important non-invasive and non-irritating testing method in distinguishing asthma from VCD [43]. In our clinical experience, most patients with VCD tend to have a low exhaled nitric oxide level while many asthmatics tend to have an elevated exhaled nitric oxide level.

Other methods have also been suggested to aid in the diagnosis of VCD including impulse oscillometry (IOS) with higher amplitude and more variable spikes on IOS impedance during inspiration in VCD subjects [44]. IOS may offer an option for evaluation in younger children. We have not yet utilized this method in our practice. Another method, high-resolution dynamic volume CT,

demonstrated 78.2% luminal reduction of the larynx in those with VCD compared to 10.4% in those without VCD [18]. These findings were noted during expiration, not inspiration, in the majority of subjects. More research will need to be performed before this imaging method is accepted into clinical practice.

Therapeutic options

Although asthma and VCD may have similar triggers and symptoms, the treatment approach for VCD is very different than treatments used to manage and control asthma. It has been the authors' observation that many patients, after suffering for years with symptoms unresponsive to previous treatments, will experience therapeutic "catharsis" after learning about their VCD diagnosis and prognosis. Therefore, diagnostic precision in conjunction with optimal therapeutics is a prerequisite for the best patient outcomes in this patient population. Asthma and VCD share many comorbidities and environmental triggers that can exacerbate each disease. Hence, the treatment of underlying coexisting medical conditions and removal of triggers are helpful in both conditions. Furthermore, there has been a significant progress in identifying various asthma phenotypes which have guided therapies (for example, anti-IgE monoclonal antibody in allergic asthma or anti-IL5 monoclonal antibodies in type 2 high/eosinophilic asthma). While attempts have been made to phenotype VCD, the association between VCD phenotypes and targeted therapies has not been yet established. The standard therapeutic options for VCD include reassurance, breathing exercises, and speech therapy. Other therapies that have been proposed include psychotherapy, biofeedback, and medical therapies. While various treatment strategies have been used, rigorous controlled studies are lacking. Therefore, VCD is usually best managed through an interdisciplinary approach [45].

Acute treatment

It is important to be aware that VCD can manifest with acute onset of symptoms and attacks which may appear similar to acute respiratory failure or severe asthma exacerbation. During an acute episode, the authors recommend reassurance and supportive care until the episode abates. Asking the patient to utilize breathing exercises may help stop the episode. The common breathing techniques include pursed lip breathing, panting, three sniffs, nose-to-mouth breathing, abdominal breathing, and jaw thrust which all help relax or open the vocal cords [46]. In more refractory cases, the use of continuous positive airway pressure (CPAP) may be helpful. In a patient with VCD, CPAP lowers expiratory flow, increases lung volume, opens the glottis, and reduces the effort needed for inspiration by establishing a favorable pressure gradient for inhalation [47, 48].

While it is clear that VCD is not a disease of the lungs and patients do not require supplemental oxygen, in a small case series, 4 out of 5 pediatric patients with VCD were treated with an 80% helium/20% oxygen mixture (Heliox) with a clinical benefit [49]. In some severe cases of VCD-induced respiratory distress and when the VCD diagnosis is unknown, the patients will undergo endotracheal intubation or even tracheostomy [50]. It is our opinion that these invasive procedures should be avoided and performed only if the patient is at risk for

airway obstruction from some other causes and has concomitant VCD. If a patient is intubated for VCD, they are typically easy to ventilate unlike the patient with status asthmaticus.

Topical lidocaine applied to the larynx may be useful in some patients during acute VCD flares [51]. In our clinic, we have found that use of nebulized lidocaine (1 ml of 4% topical lidocaine mucosal solution mixed with 1 ml of saline) has good clinical efficacy with relatively fast onset of action in select patients. The proposed mechanism of action is to anesthetize the upper airway and decrease closure of the vocal cords. One should use this treatment judiciously due to the potential for lidocaine toxicity. Additionally, mild sedatives such as benzodiazepines have also been used in treatment of acute VCD attacks [46]. In our practice, we prefer to use oral benzodiazepines if patients can tolerate this route. In more severe cases, where patients are unable to take oral medications due to severe respiratory distress, we have used IV lorazepam. However, IV dosing should be administered cautiously due to the risk of respiratory drive suppression.

Chronic therapies

Coexistent VCD and asthma

As discussed previously, the initial step is determining whether a patient has VCD only or VCD in conjunction with asthma. VCD symptoms typically do not respond to asthma treatments and can actually be exacerbated by an inhaler use. We have showed that VCD can impact scoring on asthma control questionnaire, which may further complicate assessment of asthma control. Interestingly, asthmatics scored significantly higher on the question about the nocturnal symptoms and wheezing compared to the VCD patients while other responses did not distinguish the two groups [15]. Additionally, we have found that comorbid VCD and asthma lead to a significant increase in the frequency of long-acting β -agonist use compared with asthmatics alone despite a lack of difference in asthma severity between the two groups [10]. Furthermore, Tay et al. demonstrated that comorbid VCD can worsen asthma quality of life [52]. Therefore, education on the symptoms for each disease and proper asthma management may help the patient understand which symptoms are due to VCD and which are due to asthma. It is also important that the patients with coexistent VCD and asthma receive standard asthma treatment according to the GINA guidelines and the NAEPP EPR3 guidelines [53, 54].

Our experience also suggests that a substantial number of VCD patients are misdiagnosed as having asthma. Importantly, VCD subjects who had been misdiagnosed with asthma had significantly more health care utilization (ED visits, "exacerbations" treated with systemic steroids) and asthma medication use (ICS, LABAs, SABAs, and leukotriene modifiers) compared to VCD subjects who had not mimicked asthma [10, 15]. Subsequent analysis comparing these two groups showed increased medication costs of up to US \$257 monthly if a subject was misprescribed asthma medications [15]. Thus, for those who are misdiagnosed as asthma and only have VCD, the authors recommend that the asthma therapies are stopped and that the asthma diagnosis is removed from the patient's medical record in order to avoid unnecessary medications, procedures, and health care costs.

Treatment of comorbidities

As mentioned above, if a VCD patient does have coexisting asthma, then asthma treatment should be continued. Similarly, in asthma, the use of screening questionnaires has facilitated identification of comorbid conditions including VCD [55]. Likewise, if the patient with VCD has underlying allergic rhinitis or GERD, then these conditions should be treated as they may trigger VCD symptoms by increasing laryngeal hyperresponsiveness [6, 20•, 56]. In our patient population, subjects with coexistent asthma and VCD were more likely to be using therapy with a proton pump inhibitor than those with asthma alone [10]. However, one needs to be vigilant regarding the duration of empiric treatment of these comorbid conditions and consider stopping treatment if there is no clinical response [57]. Additional tests, such as ambulatory reflux monitoring (pH or impedance-pH) or allergy testing (if not previously done), may be needed if the diagnosis of a comorbid condition is in question [58].

Respiratory retraining

Treatment for VCD typically involves the use of speech exercises that relax the throat muscles. In our practice, for all patients who have evidence of VCD, we provide an educational handout that includes a set of breathing exercises. In our retrospective review of 89 subjects with VCD, 76.4% (68) reported improvement in symptoms when implementing the breathing exercises alone without any additional training. We further quantified the number of VCD symptomatic episodes in 15 subjects before and after providing both medical treatment and breathing exercises. After an average of 2-month telephone follow-up, these subjects reported a significant decrease in monthly episodes [15]. If symptoms are not relieved with treatment of medical comorbidities and breathing exercises, then we refer our patients to speech therapy. Speech and language therapists can instruct patients on methods of throat relaxation and suppression of throat clearing, throat tightness, dyspnea, and cough. These interventions have been found to be beneficial in decreasing laryngeal hypersensitivity and VCD symptoms, following speech pathology intervention [28, 59]. Finally, it should be noted that breathing exercises have been also utilized in patients with asthma. According to the GINA guidelines, breathing exercises are recommended as a useful supplement to asthma pharmacotherapy (class B evidence). We are not aware if these patients have been evaluated for the presence of VCD [54].

Psychological interventions

As underlying anxiety, history of sexual abuse, depression, panic and conversion disorders, and posttraumatic stress disorder have been all associated with VCD, assistance from psychologists may help to reassure patients and reduce their symptoms [60]. Psychotherapy, relaxation, and biofeedback techniques as well as anti-depressants and anxiolytics may be helpful. Most reported studies are small case series, and there are no data supporting one preferential treatment mode [61]. Of note, stress has also been associated with increased asthma morbidity [62, 63]. However, there is a lack of evidence that relaxation therapies are helpful in the management of asthma [64].

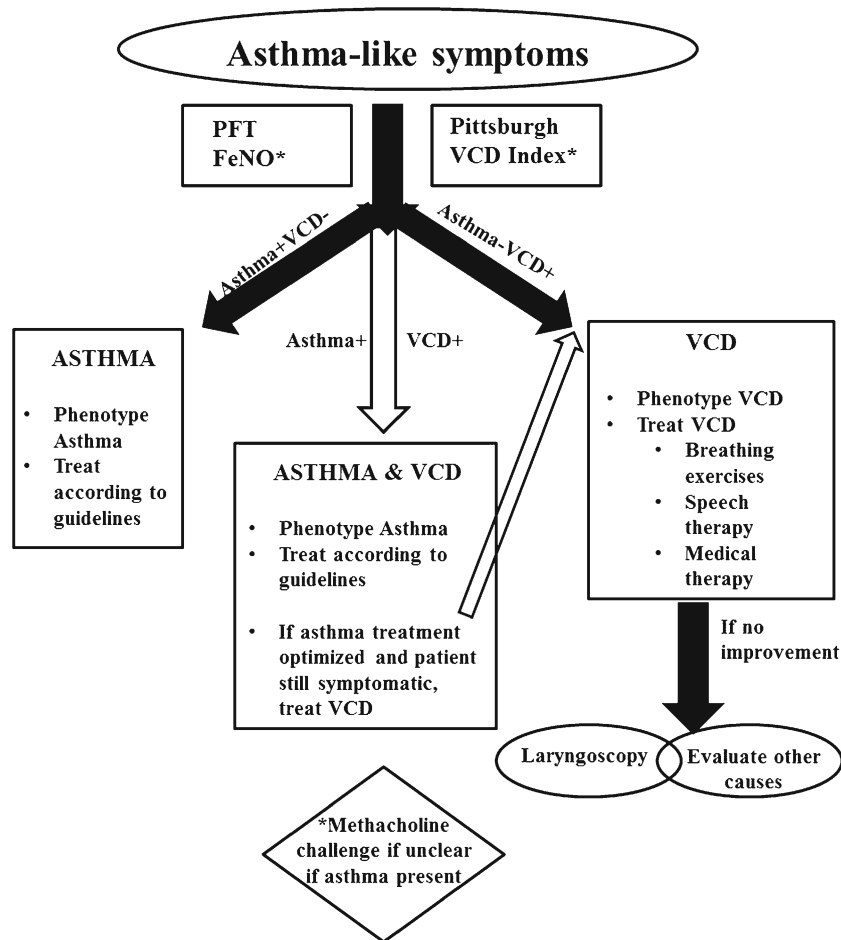


Fig. 1. Vocal cord dysfunction diagnosis and treatment algorithm.

Other therapies

The literature has reported several other therapeutic options for VCD although most of these are limited to case series. In a case series of 62 patients (age 18 to 90 years) with confirmed VCD, low-dose amitriptyline was effective in 90% of cases and most effective in patients whose symptoms had been present for less than 12 months [65]. This treatment, in conjunction with psychotherapeutic and behavioral therapies, may reduce unnecessary health care utilization. We have also found that low-dose amitriptyline is helpful in patients who have not responded to breathing exercises alone. It is also noteworthy that gabapentin and speech therapy have been recommended for treatment of chronic unexplained cough in the latest guidelines [66••]. While botulinum toxin injections have been used successfully for muscle tension dysphonia, in severe cases of VCD, botulinum toxin injections have had mixed results [67, 68]. Baxter et al. also reported improvement after botulinum toxin injections in subjects who had asthma resistant to treatment and abnormal vocal cord movement [69]. There is currently no consensus regarding the location and dosage of botulinum toxin injections, and the potential side effects include dysphonia and dysphagia.

For VCD associated with exercise, speech therapy and psychological counseling may be helpful. In a case series of patients with exercise-induced VCD, six patients pretreated with the inhaled anti-cholinergic, ipratropium, found that it prevented VCD when used prior to exercise [70]. These data suggest that much like asthma, specific phenotypes of VCD may exist and could help to guide therapy. Future, larger controlled studies are needed.

Conclusions

Accurate diagnosis of VCD is essential for the successful management of patients who present with asthma-like symptoms. Long-term management involves a multidisciplinary approach which may include physicians, speech therapists, and often psychosocial and vocational counselors. Additionally, patient's engagement and acceptance of alternative or coexistent diagnoses are of crucial importance. Distinguishing VCD from asthma can be difficult, but there are many diagnostic techniques currently available to practitioners. Our approach is depicted in Fig. 1 and Table 1.

Future directions include the better identification of specific phenotypes of VCD and their corresponding treatments. Ultimately, large prospective randomized studies will be needed to evaluate the efficacy of various treatment regimens. Additionally, increasing the awareness of VCD as a distinct clinical entity among health care providers will enhance early recognition and diagnosis of this condition and prevent unnecessary morbidity and health care utilization.

Compliance with Ethical Standards

Conflict of Interest

Dr. Andrej Petrov declares that he has no conflict of interest. Dr. Russell Traister declares that he has no conflict of interest. Dr. Merritt Fajt declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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