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Infections Including SARS-CoV-2 as Triggers for Vocal Cord Dysfunction

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Abstract

Vocal cord dysfunction (VCD) is often under-recognized and/or misdiagnosed as asthma. Although post-viral syndrome has been suggested as a contributing factor in VCD, there is limited data on infection-associated VCD. The purpose of this study was to assess and describe the proportion of patients who were diagnosed with VCD who did and did not report infection preceding VCD diagnosis. Subjects age ≥ 12 years referred for VCD assessment at the time of provocation challenge-rhinolaryngoscopy were enrolled in this prospective study of triggers for VCD registry. Enrollment initiated September 2021. An investigator designed questionnaire of potential triggers for VCD including SARS-CoV-2 was administered with medical data collection using REDCap software platform. Characteristics of subjects with and without respiratory infection-associated VCD were analyzed using Chi-square test and Student's t-test. Of the 54 subjects analyzed, 57.4% (N=31) reported infection-associated VCD symptoms with either 1) VCD onset following respiratory infection (N=18, 33.3%) or 2) VCD symptoms worsened following SARS-CoV-2 infection (N=13, 24.1%). Subjects with infection-associated and non-infection-associated VCD otherwise shared largely similar characteristics. There were more subjects being age greater than 40 years in the infection-associated group (p=0.027) and this group also reported more throat clearing (p=0.019). Our results suggest a role for infectious etiologies, including SARS-CoV-2, in triggering and/or worsening VCD. VCD should be considered in the differential diagnosis of protracted shortness of breath following SARS-CoV-2 and other respiratory infections.

Keywords

vocal cord dysfunction; post-infection syndrome; post-viral syndrome; SARS-CoV-2

Vocal cord dysfunction (VCD) is a cause of acute and/or chronic respiratory symptoms. VCD, also called inducible laryngeal obstruction and paradoxical vocal fold movement, is the functional closure of vocal cords during inspiration diagnosed by direct visualization

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by rhinolaryngoscopy (RLG) when the patient is symptomatic, typically induced by bronchoprovocation challenges including methacholine inhalation or exercise. VCD is a common functional disorder that is often under recognized and misdiagnosed as asthma. It was estimated that 42% of patients with VCD were previously misdiagnosed as having asthma for an average of 9 years [1], associated with increased healthcare costs [2]. Whereas laryngoscopy preceded by bronchoprovocation is the gold standard for diagnosis, findings may be normal in between episodes.

Although psychiatric disorders or history of physical abuse were originally associated with VCD [3], reflux disease, post-nasal drip, exercise, and respiratory irritants have been implicated [4, 5]. Post-infection syndromes have also been suggested with VCD but are not well-described. A 2004 case series described VCD following viral infections in 3 subjects [6] and a case report described VCD following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [7]. Thus, the purpose of this study was to assess and describe the proportion of patients who were diagnosed with VCD who did and did not report infection preceding VCD diagnosis.

Subjects age ≥ 12 years referred for VCD assessment at the time of provocation challenge (i.e., methacholine or exercise challenge)-RLG at the University of Nebraska Medical Center were consented and enrolled in this Institutional Review Board approved prospective observational VCD registry by their allergist, all contributing authors. Chart review/data entry conducted by JL (non-treating allergist). Subjects were without infection for at least 4 weeks prior to RLG per institutional policy and were enrolled from September 2021 to June 2023.

The subjects were administered an investigator-designed REDCap survey (available upon request) with questions regarding triggers for VCD, symptoms and comorbidities. Allergists conducting RLG were blinded to answers. On questionnaire, if subjects answered yes to 1) symptoms that led to rhinolaryngoscopy started following an infection or 2) new or worsening shortness of breath started following SARS-CoV-2 infection, they were characterized as infection-associated VCD. Demographics and clinical data including results of RLG (“positive” defined by adduction of vocal cords on inspiration), provocation challenge (Aerosol Provocation System, 5 accumulative stages of methacholine [μg:1.81, 9.07, 38.1, 154.2, 618.7], positivity defined by 20% decrease in FEV_1 as compared to baseline), spirometry, SARS-CoV-2 testing and vaccination were abstracted from patients’ medical records. Comparisons of categorical data and continuous data between the 2 groups were performed using the Chi-square test and Student’s T test, respectively, as data was normally distributed using GraphPad Prism (version 10).

A total of 71 subjects were consented for this registry. Of the 71 subjects, 4 did not complete the survey and 4 were diagnosed with alternative disorders including asthma without VCD with a positive methacholine challenge (N=3) and vocal cord granuloma (N=1). Of the 63 remaining, 54 with RLG-confirmed VCD were included for analysis. Nine subjects excluded by normal RLG. Provocation challenges were methacholine (N=50 completed, 1 uncompleted due to symptoms, 1 disqualified as FEV_1<70%) and exercise

(N=2). Characteristics of all subjects and those with and without infection associated VCD are summarized in Tables 1 and 2.

Of these 54 subjects, 31 (57.4%) reported infection-associated VCD symptoms with either 1) onset following respiratory infection (N=18, 33.3%) or 2) worsened following SARS-CoV-2 infection (N=13, 24.1%). Most subjects were white females with an average age of 49 years. The most common reported respiratory symptoms for all subjects were post-nasal drainage (88.9%), throat clearing (83.3%), shortness of breath with activity (81.4%), and cough (79.6%). The most common reported trigger was activity and sports (74.1%). Despite respiratory symptom reports, the mean spirometry assessments were normal (forced expiratory volume in one second [FEV_1]% predicted: 97.6%, forced vital capacity [FVC]% predicted: 100.9%). There were high rates of mental health disorders with 70.4% reporting either depression, anxiety, post-traumatic stress disorder, or bipolar disorder. Interestingly, subjects reported high rates of prior all-cause intubation (64.8%). Additionally, 38.9% self-reported co-morbid asthma and 51.9% self-reported gastroesophageal reflux disease (GERD). Subjects with infection-associated and non-infection-associated VCD otherwise share similar characteristics. There were more subjects age > 40 years in the infection-associated group ($p = 0.027$).

In this study post-infection associated VCD was reported by the majority (57.4%) of subjects with VCD with 13 of these 31 subjects (24.1%) reporting worsening of symptoms following SARS-CoV-2 infection. Thus, an evaluation for VCD should be considered in the differential diagnosis for those individuals with persistent symptoms of cough and shortness of breath following respiratory infections including SARS-CoV-2, particularly for those without significant abnormalities demonstrated with lung function assessments. Consistent with studies >10 years ago, our subjects with VCD were mostly females, aged 40–50 years with high rates of GERD and approximately 39% of VCD patients had co-existent asthma [1]. However, conclusions from this study may not be generalizable as this population was largely Caucasian (91%), had high rates of mental health disorders (70%) and prior intubation (65%), and infection history, including SARS-CoV-2, was self-reported. The possibility of life stressors, including anxiety of a SARS-CoV-2 infection, could have contributed to VCD symptoms. Recall bias in attributing past viral infections to VCD is also a limitation given the interval of symptoms. Post-COVID syndrome could have also been responsible for respiratory symptoms. Whereas the mechanisms underlying VCD pathogenesis remain poorly understood, it has been suggested that sensory hyperresponsiveness of the larynx due to irritants (which could be extended to post-infection inflammation) as well as cortical level activation with psychogenic triggers may be central to VCD pathogenesis [8]. It has also been suggested that viral infections can induce a cough by selectively altering neural signaling [9]. In summary, clinical awareness of the high association of post-viral syndrome and VCD is warranted to provide appropriate diagnosis and therapeutic care. We anticipate that future studies will focus on the role of various infections, degree and severity of infections, and more to better understand the role of respiratory infections preceding VCD.

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REFERENCES

1. Traister RS, Fajt ML, Whitman-Purves E, Anderson WC, Petrov AA. A retrospective analysis comparing subjects with isolated and coexistent vocal cord dysfunction and asthma. Allergy Asthma Proc. 2013;34(4):349–55. [PubMed: 23883599]
2. Traister RS, Fajt ML, Petrov AA. The morbidity and cost of vocal cord dysfunction misdiagnosed as asthma. Allergy Asthma Proc. 2016;37(2):25–31. [PubMed: 26932166]
3. Patterson R, Schatz M, Horton M. Munchausen's stridor: non-organic laryngeal obstruction. Clin Allergy. 1974;4(3):307–10. [PubMed: 4426113]
4. Forrest LA, Husein T, Husein O. Paradoxical vocal cord motion: classification and treatment. Laryngoscope. 2012;122(4):844–53. [PubMed: 22434681]
5. George S, Suresh S. Vocal Cord Dysfunction: Analysis of 27 Cases and Updated Review of Pathophysiology & Management. Int Arch Otorhinolaryngol. 2019;23(2):125–30. [PubMed: 30956693]
6. Taramarcaz P, Grissell TV, Borgas T, Gibson PG. Transient postviral vocal cord dysfunction. J Allergy Clin Immunol. 2004;114(6):1471–2. [PubMed: 15577854]
7. Garg A, Peterson BE, Comellas AP. Post-COVID-19 Vocal Cord Dysfunction. Am J Respir Crit Care Med. 2022;206(2):e4–e6. [PubMed: 35649174]
8. Leong P, Gibson PG, Vertigan AE, Hew M, McDonald VM, Bardin PG. Vocal cord dysfunction/inducible laryngeal obstruction-2022 Melbourne Roundtable Report. Respirology. 2023;28(7):615–26. [PubMed: 37221142]
9. Footitt J, Johnston SL. Cough and viruses in airways disease: mechanisms. Pulm Pharmacol Ther. 2009;22(2):108–13. [PubMed: 19480062]

Clinical Implications:

Post-infection syndrome has been suggested as a trigger for vocal cord dysfunction (VCD) but to date there has been little data supporting this observation. This study suggests a role for respiratory infectious etiologies, including SARS-CoV-2, in the development of VCD.

Table 1.

Viral associations and Demographics of VCD Subjects

Characteristics	All Subjects (N=54)	Infection Associated (N=31)	Non-Infection Associated (N=23)	p-value
Infection-associated VCD, N (%)	31 (57.4)			
Initiated with non-SARS-CoV-2 Infection	18 (33.3)			
Symptoms worsened after SARS-CoV-2	13 (24.1)			
History of SARS-CoV-2 Infection*, N (%)	27 (50.0)	23 (74.2)	4 (17.3)	**<0.0001**
Symptoms worsened by SARS-CoV-2	13 of 27 (48.1)	13 of 23 (56.5)	0 of 4 (0)	
Vaccinated for SARS-CoV-2, N (%)	47 (87.0)	25 (81.0)	22 (95.7)	0.105
Age in years, mean (range)	49.3 (17–79)	52.9 (17–79)	45.7 (20–76)	0.109
Age > 40, N (%)	39 (72.2)	26 (83.9)	13 (56.5)	**0.027**
Age of symptom onset in years, mean (SD)	39.0 (18.5)	42.2 (17.3)	34.8 (19.7)	0.148
Time, in years, mean (SD)	10.9 (14.2)	10.8 (14.7)	11.1 (13.8)	0.936
Sex, Female, N (%)	46 (85.2)	25 (80.7)	21 (91.3)	0.276
Race and Ethnicity, N (%)				0.682
Non-Hispanic White	49 (90.7)	29 (93.5)	20 (87.0)	
Non-Hispanic Black	2 (3.7)	1 (3.2)	1 (4.3)	
Hispanic White	1 (1.9)	0 (0)	1 (4.3)	
Other	2 (3.7)	1 (3.2)	1 (4.3)	
Body mass index, mean (SD)	31.7 (8.3)	32.3 (8.5)	31.5 (7.8)	0.728
Current/former smoker, N (%)	17 (31.5)	11 (35.5)	6 (26.1)	0.462
Current smoker	2 (3.7)	2 (6.5)	0 (0)	
Former smoker	15 (27.8)	9 (29.0)	6 (26.1)	
Previously intubated, N (%)	35 (64.8)	20 (64.5)	15 (65.2)	0.957
Previous military deployment, N (%)	5 (9.3)	3 (9.6)	2 (8.7)	0.902
Asthma (self-reported), N (%)	21 (38.9)	11 (35.5)	10 (43.5)	0.551
Positive methacholine challenge	15 of 19 (78.9)†	6 of 9 (66.7)†	9 of 10 (90.0)	0.339
Positive exercise challenge	0 of 1 (0)	0 of 1 (0)		
FEV_1% predicted, mean (SD)	97.6 (13.1)	97.7 (15.2)	97.5 (9.4)	0.970
FVC% predicted, mean (SD)	100.9 (13.5)	100.6 (14.4)	101.3 (12.3)	0.848
Flat inspiratory loop on PFTs, N (%)	22 (40.7)	13 (41.9)	9 (39.1)	0.836
Methacholine cumulative dose, µg, mean (SD)#	680 (390)	720 (360)	630 (410)	0.390
GERD, N (%)	28 (51.9)	17 (54.8)	11 (47.8)	0.610
Allergies, N (%)	39 (72.2)	22 (71.0)	17 (73.9)	0.811
Pittsburgh VCD Index score, mean (SD)	5.9 (2.6)	5.7 (2.8)	6.2 (2.4)	0.501
History of mental health diagnosis, N (%)	38 (70.4)	23 (74.2)	15 (65.2)	0.475
Anxiety	26 (48.1)	16 (51.5)	10 (43.5)	0.554
Depression	27 (50.0)	15 (48.4)	12 (52.2)	0.783
Bipolar disorder	4 (7.4)	1 (3.2)	3 (13.0)	0.173
PTSD	15 (27.8)	8 (25.8)	7 (30.4)	0.707

Characteristics	All Subjects (N=54)	Infection Associated (N=31)	Non-Infection Associated (N=23)	p-value
History of domestic violence, N (%)	14 (26.0)	9 (29.0)	5 (21.7)	0.545

Statistical significance ($p<0.05$) between infection and non-infection associated VCD are bolded.

*asterisks denote SARS-CoV-2 infection was self-reported.

†1 self-reported asthmatic did not have methacholine challenge due to baseline FEV_1<70%.

#N=50 completed methacholine challenges (1 disqualified as baseline FEV_1<70%, 1 aborted due to patient difficulties in conducting challenge, 2 underwent exercise challenge with negative results as a positive was defined as a drop of FEV_1 by 10% from baseline).

Table 2.

Symptoms and Triggers of VCD Subjects

Characteristics	All Subjects (N=54)	Infection Associated (N=31)	Non-Infection Associated (N=23)	p-value
Symptom location, N (%)				0.055
Neck alone	10 (18.5)	5 (16.1)	5 (21.7)	
Chest alone	12 (22.2)	10 (32.2)	2 (8.7)	
Both neck and chest	20 (37.0)	8 (25.8)	12 (52.2)	
Respiratory symptoms, N (%)				
Shortness of breath at rest	29 (53.7)	16 (51.6)	13 (56.5)	0.721
Shortness of breath with activity	44 (81.4)	24 (77.4)	20 (87.0)	0.372
Cough	43 (79.6)	26 (84.0)	17 (73.9)	0.369
Throat clearing	45 (83.3)	29 (93.5)	16 (69.6)	**0.019**
Throat tightness	34 (63.0)	19 (61.3)	15 (65.2)	0.768
Chest tightness	33 (61.1)	17 (54.8)	16 (69.6)	0.272
Wheezing	31 (57.4)	18 (58.1)	13 (56.5)	0.910
Difficulty getting air in	36 (66.7)	21 (67.8)	15 (65.2)	0.846
Difficulty getting air out	15 (27.7)	10 (32.3)	5 (21.7)	0.394
Hoarseness	34 (63.0)	21 (67.7)	13 (56.5)	0.399
Heartburn	28 (51.9)	13 (41.9)	15 (65.2)	0.090
Recurrent sinus infections	22 (40.7)	15 (48.4)	7 (30.4)	0.184
Post-nasal drainage	48 (88.9)	29 (93.5)	19 (82.6)	0.206
Triggers, N (%)				
Activity/sports	40 (74.1)	23 (74.2)	17 (73.9)	0.981
Mental Stress/Stress situations	28 (51.9)	18 (58.1)	10 (43.4)	0.289
Temperature change	31 (57.4)	17 (54.8)	14 (60.9)	0.658
Odors	24 (44.4)	12 (38.7)	12 (52.2)	0.325
Foods	11 (20.3)	7 (22.6)	4 (17.3)	0640
# of triggers increasing with time, N (%)	32 (59.3)	17 (54.8)	15 (65.2)	0.443

Statistical significance ($p<0.05$) between infection and non-infection associated VCD is bolded.