Infections including SARS-CoV-2 as triggers for vocal cord dysfunction

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Clinical Implications

Postinfection syndrome has been suggested as a trigger for vocal cord dysfunction, but to date, there have been little data supporting this observation. This study suggests a role for respiratory infectious etiologies, including severe acute respiratory syndrome coronavirus 2, in the development of vocal cord dysfunction.

Vocal cord dysfunction (VCD) is a cause of acute and/or chronic respiratory symptoms. Vocal cord dysfunction, also called inducible laryngeal obstruction and paradoxical vocal fold movement, is the functional closure of vocal cords during inspiration diagnosed by direct visualization by rhinolaryngoscopy (RLG) when the patient is symptomatic, typically induced by bronchoprovocation challenges including methacholine inhalation or exercise. Vocal cord dysfunction is a common functional disorder that is often underrecognized 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 health care 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, postnasal drip, exercise, and respiratory irritants have been implicated.[4,5] Postinfection 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 and older referred for VCD assessment at the time of provocation challenge (ie, 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 was conducted by J. L. (nontreating 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 Research Electronic Data Capture (REDCap) survey (available upon request) with questions regarding triggers for VCD, symptoms, and comorbidities. Allergists conducting RLG were blinded to answers. On the questionnaire, if subjects answered yes to (1) symptoms that led to RLG 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 forced expiratory volume in 1 second [FEV_1] compared with 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 χ^2 test and Student *t* test, respectively, as data were 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 were 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 I and II.

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 postnasal 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 (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, posttraumatic stress disorder, or bipolar disorder. Interestingly, subjects reported high rates of prior all-cause intubation (64.8%). In addition, 38.9% self-reported comorbid asthma and 51.9% self-reported gastroesophageal reflux disease. Subjects with infection-associated and non—infection-associated VCD otherwise share similar characteristics. There were more subjects age older than 40 years in the infection-associated group ($P = 0.027$).

In this study, postinfection-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 from more than 10 years ago, our subjects with VCD were mostly females, aged 40

TABLE I. 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)	**<.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)	.105
Age (y), mean (range)	49.3 (17−79)	52.9 (17−79)	45.7 (20-76)	.109
>40, n (%)	39 (72.2)	26 (83.9)	13 (56.5)	**.027**
Age of symptom onset (y), mean (SD)	39.0 (18.5)	42.2 (17.3)	34.8 (19.7)	.148
Time (y), mean (SD)	10.9 (14.2)	10.8 (14.7)	11.1 (13.8)	.936
Sex, female, n (%)	46 (85.2)	25 (80.7)	21 (91.3)	.276
Race and ethnicity, n (%)				.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)	.728
Current/former smoker, n (%)	17 (31.5)	11 (35.5)	6 (26.1)	.462
Current	2 (3.7)	2 (6.5)	0 (0)	
Former	15 (27.8)	9 (29.0)	6 (26.1)	
Previously intubated, n (%)	35 (64.8)	20 (64.5)	15 (65.2)	.957
Previous military deployment, N (%)	5 (9.3)	3 (9.6)	2 (8.7)	.902
Asthma (self-reported), n (%)	21 (38.9)	11 (35.5)	10 (43.5)	.551
Positive methacholine challenge	15 of 19 (78.9)‡	6 of 9 (66.7)‡	9 of 10 (90.0)	.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)	.970
FVC% predicted, mean (SD)	100.9 (13.5)	100.6 (14.4)	101.3 (12.3)	.848
Flat inspiratory loop on PFTs, n (%)	22 (40.7)	13 (41.9)	9 (39.1)	.836
Methacholine cumulative dose (μg), mean (SD)§	680 (390)	720 (360)	630 (410)	.390
GERD, n (%)	28 (51.9)	17 (54.8)	11 (47.8)	.610
Allergies, n (%)	39 (72.2)	22 (71.0)	17 (73.9)	.811
Pittsburgh VCD index score, mean (SD)	5.9 (2.6)	5.7 (2.8)	6.2 (2.4)	.501
History of mental health diagnosis, n (%)	38 (70.4)	23 (74.2)	15 (65.2)	.475
Anxiety	26 (48.1)	16 (51.5)	10 (43.5)	.554
Depression	27 (50.0)	15 (48.4)	12 (52.2)	.783
Bipolar disorder	4 (7.4)	1 (3.2)	3 (13.0)	.173
PTSD	15 (27.8)	8 (25.8)	7 (30.4)	.707
History of domestic violence, n (%)	14 (26.0)	9 (29.0)	5 (21.7)	.545

FVC, Forced vital capacity; *GERD,* gastroesophageal reflux disease; *PFT,* pulmonary function tests; *PTSD,* posttraumatic stress disorder.
*Statistical significance ($P < .05$) between infection- and non−infection-associated VCD is set in bold.
†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 because a positive was defined as a drop of FEV_1 by 10% from baseline).

to 50 years with high rates of gastroesophageal reflux disease and approximately 39% of VCD patients had coexistent asthma.[1] However, conclusions from this study may not be generalizable because this population was largely Caucasian (91%), with 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−coronavirus disease 2019 (COVID-19) 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 postinfection 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 postviral syndrome and VCD is warranted to provide appropriate diagnosis and therapeutic care. We anticipate that future studies will

TABLE II. 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 (%)				.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)	.721
Shortness of breath with activity	44 (81.4)	24 (77.4)	20 (87.0)	.372
Cough	43 (79.6)	26 (84.0)	17 (73.9)	.369
Throat clearing	45 (83.3)	29 (93.5)	16 (69.6)	**.019**
Throat tightness	34 (63.0)	19 (61.3)	15 (65.2)	.768
Chest tightness	33 (61.1)	17 (54.8)	16 (69.6)	.272
Wheezing	31 (57.4)	18 (58.1)	13 (56.5)	.910
Difficulty getting air in	36 (66.7)	21 (67.8)	15 (65.2)	.846
Difficulty getting air out	15 (27.7)	10 (32.3)	5 (21.7)	.394
Hoarseness	34 (63.0)	21 (67.7)	13 (56.5)	.399
Heartburn	28 (51.9)	13 (41.9)	15 (65.2)	.090
Recurrent sinus infections	22 (40.7)	15 (48.4)	7 (30.4)	.184
Postnasal drainage	48 (88.9)	29 (93.5)	19 (82.6)	.206
Triggers, n (%)				
Activity/sports	40 (74.1)	23 (74.2)	17 (73.9)	.981
Mental stress/stress situations	28 (51.9)	18 (58.1)	10 (43.4)	.289
Temperature change	31 (57.4)	17 (54.8)	14 (60.9)	.658
Odors	24 (44.4)	12 (38.7)	12 (52.2)	.325
Foods	11 (20.3)	7 (22.6)	4 (17.3)	.640
Triggers increasing with time, n (%)	32 (59.3)	17 (54.8)	15 (65.2)	.443

*Statistical significance ($P < .05$) between infection- and non−infection-associated VCD is set in bold.

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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