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Vocal cord dysfunction/inducible laryngeal obstruction(s) mimicking anaphylaxis during SARS-CoV-2 (COVID-19) vaccination

Paul Leong, PhD[a,b], Mohammed Al-Harrasi, MD[a], Beau Carr, MBBS[a], Elizabeth Leahy, BN[a], Phillip G. Bardin, PhD[a,b,*], and Sara Barnes, FRACP[a,b,*]

Clinical Implications

Dyspnea, tachypnea, and throat tightness following vaccination provoke concern for anaphylaxis, but these symptoms are also characteristic of vocal cord dysfunction/inducible laryngeal obstruction. We report the first case series of vocal cord dysfunction/inducible laryngeal obstruction occurring in the context of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease 2019 [COVID-19]) vaccination.

The Brighton Collaboration anaphylaxis definition includes symptoms of respiratory distress, tachypnea, hoarse voice, stridor, and a sensation of throat closure.[1] These features significantly overlap with manifestations of vocal cord dysfunction/inducible laryngeal obstruction(s) (VCD/ILO), a disorder characterized by intermittent laryngeal obstruction.[2] We have recently proposed cardinal VCD/ILO phenotypes, including incident-associated VCD/ILO, which may be linked to vaccination.[3]

This Clinical Communication details the first case series of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease 2019 [COVID-19]) vaccination-related VCD/ILO in 10 consecutive individuals who were initially labelled as having only anaphylaxis. The study received ethics authorization from Monash Health (QA/80480/MonH-2021-289442).

In the local health care setting, individuals receive SARS-CoV-2 vaccination in primary care, hospital clinics, or vaccine hubs. Following a provisional diagnosis of anaphylaxis to a SARS-CoV-2 vaccine, individuals are referred to a subspecialist vaccine reaction assessment service located at a tertiary-care hospital (Monash Health). After initial assessment by a specialist allergist/immunologist, a second dose of the same brand of SARS-CoV-2 vaccine may be administered under supervision in the allergy/immunology clinic.

During March 2021 to December 2021, 149 people were assessed in the vaccine reaction clinic. Details of 10 consecutive symptomatic individuals who generated a strong clinical suspicion for VCD/ILO are reported here. The median age was 33 years (interquartile range 31−54 y) and all were female. Notably, 8 of the 10 patients reported a history of anaphylaxis (penicillin, foods, and insect venoms), with 6 having been treated with epinephrine prior to receiving SARS-CoV-2 vaccination. A history of asthma was present in 6 patients and 4 had a history of anxiety or depression.

Seven of the 10 reactions after a first dose of vaccine occurred following Pfizer-BioNTech (BNT162b2) administration and 3 of 10 following receipt of the AstraZeneca (ChAdOx1 nCoV-19/AZD1222) vaccine. Symptoms included dyspnea in all cases, a sensation of throat closure (8 of 10), and tachypnea with increased respiratory effort (8 of 10). Hoarse voice was present in 3; stridor and wheeze were present in 2 patients. In 6 patients, symptoms began within 30 minutes of the dose. All patients presented to an emergency department, and a provisional diagnosis of anaphylaxis was made by the treating physicians in all cases.

One individual had Brighton diagnostic certainty level 1 anaphylaxis with rapid onset of facial and upper airway angioedema, hypotension, and elevated tryptase (22 μg/L, upper limit of normal 11.4 μg/L). This patient was admitted to the hospital; respiratory syncytial virus was detected and subsequent inpatient laryngoscopy performed in the intensive care unit for nonresolving stridor demonstrated obvious inspiratory vocal cord adduction indicating VCD/ILO. In the other patients, laryngoscopy was not performed and symptomatic treatment was administered leading to symptom resolution.

Following specialist allergist assessment, 9 of the 10 individuals, including the patient with anaphylaxis, received a second dose of the same vaccine that caused their reaction in a monitored hospital setting. Symptoms recurred in 8 of the 9 patients who received the second vaccination and clinical findings mirrored the initial reactions. All reactions occurred within 30 minutes of vaccine administration with a sensation of throat closure in 8 of 9 patients, tachypnea in 7, stridor in 2, wheeze in 2, and hoarse voice in 1. One patient fulfilled a Brighton diagnostic certainty level 3 case definition of anaphylaxis, developing sudden-onset mild dyspnea, nausea, widespread pruritus without rash, and an itchy throat 15 minutes post dose; laryngoscopy revealed subcriterion vocal cord adduction, which did not meet formal endoscopic criteria for VCD/ILO,[2] and there was no airway edema.

In these 9 individuals, laryngoscopy was performed and no patients were found to have upper airway angioedema. However, inspiratory vocal cord adduction (>50% reduction in luminal area[2]) was observed confirming a diagnosis of VCD/ILO in 4 patients. These individuals were clinically not distinct from patients with absence of VCD/ILO on laryngoscopy.

The final patient wished to avoid readministration of the index vaccine (Pfizer-BioNTech BNT162b2) and was administered another vaccine (Moderna mRNA-1273). In summary, in 10 individuals initially diagnosed with anaphylaxis after SARS-CoV-2 vaccination, the initial diagnosis may have been correct in a small minority with only 2 cases meeting Brighton Criteria for anaphylaxis. Symptoms were concordant with incident-associated VCD/ILO, and characteristic inspiratory vocal cord closure was demonstrated in 5 patients. The remaining 5 patients had characteristic symptoms of VCD/ILO and anaphylaxis was not demonstrated. Possibilities include a missed diagnosis of VCD/ILO (ie, laryngeal movement abnormalities were not present during laryngoscopy but the patient truly had VCD/ILO) or alternatives such as anxiety and somatoform disorder.

The Brighton Criteria were originally developed for vaccination-related anaphylaxis. However, clinical features overlap with VCD/ILO and particularly a sensation of a tight throat, hoarse voice, and respiratory distress may be indistinguishable. Differentiation of lower airway from upper airway wheeze may be difficult, adding to diagnostic uncertainty.

A vaccine-reaction presentation with upper-airway dominant features (such as throat closure and stridor) without objective anaphylaxis manifestations hints at VCD/ILO, but anaphylaxis remains the major differential. Importantly, anaphylaxis and VCD/ILO can occur together. The critical investigation is laryngoscopy, which may confirm VCD/ILO with inappropriate laryngeal narrowing or demonstrate anaphylaxis-related angioedema. It is not clear why VCD/ILO occurs during vaccination but, because the larynx has key protective functions,[4] reflex responses may result in laryngeal closure during stressful situations—such as with immunization.[3,4]

There are important caveats. Definitive VCD/ILO was only directly visualized in 5 patients but symptoms in the other 5 cases were typical of VCD/ILO. This is not unexpected because VCD/ILO is typically intermittent[5] and may not have been visualized by laryngoscopy. The study was done in a single center and findings may not pertain to other locations.

No randomized treatment studies have been performed for VCD/ILO. Acute management includes reassurance, breathing strategies such as panting to facilitate glottic aperture opening, continuous positive airway pressure, and benzodiazepines.[4] In the longer term, speech-behavioral therapy is designed to regain laryngeal control.

In conclusion, clinicians should be aware that VCD/ILO can mimic anaphylaxis and that the 2 conditions may overlap. Differentiation of anaphylaxis from VCD/ILO is critical in the setting of vaccination, especially during the ongoing pandemic because diagnosing an individual with vaccine-related anaphylaxis has critical implications for future vaccination and their ability to benefit from this important treatment.

[a]Monash Lung Sleep Allergy and Immunology, Monash Health, Clayton, Victoria, Australia
[b]School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia
[*]Co-senior author.

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Corresponding author: Paul Leong, PhD, Monash Lung Sleep Allergy and Immunology, Monash Health, 246 Clayton Rd., Clayton, Victoria, Australia. E-mail: paul.leong@monash.edu.

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REFERENCES

1. Rüggeberg JU, Gold MS, Bayas J-M, Blum MD, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5675-84.
2. Morris MJ, Christopher KL. Diagnostic criteria for the classification of vocal cord dysfunction. Chest 2010;138:1213-23.
3. Leong P, Phyland DJ, Koo J, Baxter M, Bardin PG. Middle airway obstruction: phenotyping vocal cord dysfunction/inducible laryngeal obstruction(s) to progress diagnosis and management. Lancet Respir Med 2022;10:3-5.
4. Hull JH, Backer V, Gibson PG, Fowler SJ. Laryngeal dysfunction: assessment and management for the clinician. Am J Respir Crit Care Med 2016;194:1062-72.
5. Halvorsen T, Walsted ES, Bucca C, Bush A, Cantarella G, Friedrich G, et al. Inducible laryngeal obstruction: an official joint European Respiratory Society and European Laryngological Society statement. Eur Respir J 2017;50:1602221.