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

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Title: Vocal cord dysfunction/inducible laryngeal obstruction(s) mimicking anaphylaxis during SARS-CoV-2 (coronavirus) vaccination

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20 **Clinical implications box:** Dyspnoea, tachypnoea and throat tightness following vaccination provoke
21 concern for anaphylaxis but these symptoms are also characteristic of vocal cord
22 dysfunction/inducible laryngeal obstruction(s). We report the first case series of VCD/ILO occurring in
23 the context of SARS-CoV-2 (coronavirus) vaccination.

Clinical Communication

The Brighton Collaboration anaphylaxis definition includes symptoms of respiratory distress, tachypnoea, 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 characterised 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 SARS-CoV-2 (coronavirus) vaccination-related VCD/ILO in ten consecutive individuals who were initially labelled as having only anaphylaxis.

The study received ethics authorisation from Monash Health (QA/80480/MonH-2021-289442).

In the local health-care setting individuals receive coronavirus vaccination in primary care, hospital clinics or vaccine hubs. Following a provisional diagnosis of anaphylaxis to 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 ten consecutive symptomatic individuals who generated a strong clinical suspicion for VCD/ILO are reported here. Median age was 33 years (interquartile range (IQR) 31-54) and all were female. Notably, eight of the ten patients reported a history of “anaphylaxis” (penicillin, foods, and insect venoms), with six having been treated with epinephrine prior to receiving SARS-CoV-2 vaccination. A history of asthma was present in six patients and four had a history of anxiety or depression.

Seven of the ten (7/10) reactions after a first dose of vaccine occurred following Pfizer-BioNTech (BNT162b2) administration and three (3/10) following receipt of the AstraZeneca (ChAdOx1 nCoV-19/AZD1222) vaccine. Symptoms included dyspnoea in all cases, a sensation of throat closure (8/10),

and tachypnoea with increased respiratory effort (8/10). Hoarse voice was present in 3/10; stridor and wheeze were present in 2/10 patients. In 6/10 patients, symptoms began within 30 minutes of the dose. All patients presented to an Emergency Department (ED), 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 micrograms/litre, upper limit of normal 11.4 micrograms/litre). This patient was admitted to hospital, respiratory syncytial virus was detected and subsequent inpatient laryngoscopy performed in the intensive care unit for non-resolving 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, nine of the ten 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 8/9 patients who received the second vaccination and clinical findings mirrored the initial reactions. All occurred within 30 minutes of vaccine administration with a sensation of throat closure in 8/9, tachypnoea in 7/9, stridor in 2/9, wheeze in 2/9 and hoarse voice in 1/9 patients. One patient fulfilled a Brighton diagnostic certainty level 3 case definition of anaphylaxis, developing sudden-onset mild dyspnoea, nausea, widespread pruritis 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 oedema.

In these nine 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 4/9 patients. These individuals were clinically not distinct from patients with absence of VCD/ILO on laryngoscopy.

The final patient wished to avoid re-administration of the index vaccine (Pfizer-BioNTech BNT162b2) and was administered another vaccine (Moderna mRNA-1273). In summary, in ten individuals initially diagnosed with anaphylaxis after SARS-CoV-2 vaccination, the initial diagnosis may have been correct in a small minority with only two cases meeting Brighton criteria for anaphylaxis. Symptoms were concordant with 'incident-associated VCD/ILO' and characteristic inspiratory vocal cord closure was demonstrated in five patients. The remaining five patients had characteristic symptoms of VCD/ILO and anaphylaxis was not demonstrated. Possibilities include a missed diagnosis of VCD/ILO (i.e. 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 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, since the larynx has key protective functions(4), reflex responses may result in laryngeal closure during stressful situations - such as with immunisation(3,4).

There are important caveats. Definitive VCD/ILO was only directly visualised in five patients but symptoms in the other five cases were typical of VCD/ILO. This is not unexpected since VCD/ILO is typically intermittent(5) and may not have been visualised by laryngoscopy. The study was done in a single centre 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 two conditions may overlap. Differentiation of anaphylaxis from VCD/ILO is critical in the setting of vaccination, especially during the ongoing pandemic since diagnosing an individual with vaccine-related anaphylaxis has critical implications for future vaccination and their ability to benefit from this important treatment.

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