

Transient postviral vocal cord dysfunction

To the Editor:

Vocal cord dysfunction (VCD) consists of paradoxical inspiratory vocal cord adduction demonstrated by means of either fiberoptic laryngoscopy or variable extrathoracic airflow obstruction from an inspiratory flow-volume loop.^{1,2}

VCD presents with dyspnea, wheeze, stridor, and cough.^{1,2} Psychological conditions, such as conversion reactions, were initially recognized as the exclusive cause of VCD.^{1,3} Now nonpsychological conditions, such as gastroesophageal reflux,⁴ sinusitis,⁵ postnasal drip syndrome,^{5,6} and asthma,⁷ are linked to VCD.

Here we report an association between viral upper respiratory tract infection (URTI) and VCD with 2 cases of viral infection causing a transient VCD and 1 case of viral infection leading to a severe exacerbation of preexisting VCD.

Case 1: A 37-year-old man presented with typical URTI symptoms of malaise, fever, chills, myalgia, sore throat, and photophobia. The Common Cold Unit questionnaire⁸ indicated a probable viral infection. These symptoms resolved within 7 days with paracetamol. On day 8, the patient had a dry cough, constant upper chest tightness, mild inspiratory dyspnea, and husky voice. These respiratory symptoms persisted for 3 weeks. Before development of this illness, the patient had participated as a healthy control subject in a clinical study in which provocation challenge with oral inhalation of 4.5% saline demonstrated normal flow-volume curves at baseline and after provocation. Although symptomatic after the URTI, rhinolaryngoscopy was performed before and after oral inhalation of 4.5% saline. The results of baseline rhinolaryngoscopy were normal, but postsaline rhinolaryngoscopy showed paradoxical inspiratory adduction of the true vocal cords. Flow-volume curves showed a normal FEV₁, but forced inspiratory flow at 50% of vital capacity (FIF₅₀) decreased by 40%, from 10.00 L/s at baseline to 6.00 L/s after saline challenge. PCR results of a spontaneous sputum sample were positive for human metapneumovirus (hMPV).⁹ A third saline challenge 1 month after resolution of the symptoms displayed normal inspiratory flow with a nonsignificant 5% decrease in FIF₅₀, from 10.88 L/s at baseline to 10.35 L/s after challenge.

Case 2: A 45-year-old man with perennial allergic rhinitis presented with URTI, featuring myalgia, fever, sore throat, runny nose, conjunctivitis, dry cough, and mild inspiratory dyspnea. The Common Cold Unit questionnaire⁸ indicated a probable viral infection. The illness resolved in 7 days with paracetamol. Before this illness, the subject underwent oral inhalation challenge with 4.5% saline that demonstrated normal inspiratory and expiratory flow-volume curves both at baseline and after provocation. Rhinolaryngoscopy was performed during the URTI immediately before and after oral provocation with 4.5%

saline. Baseline laryngoscopy was normal, but postsaline laryngoscopy showed a paradoxical inspiratory adduction of the true vocal cords with a glottic chink. A similar saline challenge was performed 4 days after the beginning of the URTI, whereas the subject was still symptomatic. Flow-volume curves showed a normal FEV₁, but the inspiratory flow curve was attenuated after 19.85 mL of nebulized 4.5% saline, with the FIF₅₀ decreasing by 44%, from 7.85 L/s to 4.41 L/s. PCR of an induced sputum sample indicated a picornavirus infection. A third saline challenge 1 month after recovery displayed a complete normalization of the inspiratory flow curve and a decrease in FIF₅₀ from 7.27 L/s at baseline to 5.97 L/s after the saline challenge (a nonsignificant 18% reduction).

Case 3: A 50-year-old man with a prior history of confirmed VCD presented to the emergency department with severe inspiratory stridor, cough, and dyspnea in the context of a recent URTI, with chills, watery eyes, sneezing, and severe rhinitis. The Common Cold Unit questionnaire⁸ indicated a probable viral infection. Spirometry showed an FEV₁/forced vital capacity of 0.6/0.6 L, with an early cutoff suggestive of VCD. He was treated unsuccessfully with conventional asthma therapy and responded to nasal continuous positive airway pressure (CPAP) with improvement over 4 hours, but there was an immediate worsening of symptoms when CPAP was removed. Intermittent CPAP was reinstituted, and the symptoms resolved over 7 days. Induced sputum was collected, and influenza virus A was identified on the basis of both culture and PCR. On review after 2 weeks, resting flow-volume curves were normal at baseline, with an FIF₅₀ of 9.52 L/s. Subsequent inhalation challenge with 1.74 mL of hypertonic saline provoked a decrease in FIF₅₀ to 7.17 L/s (a 25% decrease from baseline). This test was terminated prematurely because of severe upper airway obstruction. The patient reported 3 similar episodes of inspiratory stridor in the context of URTIs over the past 7 years. Previous flow-volume curves during both asymptomatic and symptomatic episodes identified variable extrathoracic airflow limitation in the absence of bronchial hyperreactivity.⁶ These findings were compatible with a diagnosis of VCD.

These 3 cases provide new evidence that viral URTIs can trigger VCD. Viral URTI was found to induce transient VCD and exacerbate preexisting VCD. This is an important novel finding that might be of significance to postviral respiratory syndromes. Infections have been insufficiently investigated as a cause of VCD, and no microbiologic assessments are published. Bucca et al⁵ demonstrated that during an exacerbation of chronic sinusitis, most subjects had variable extrathoracic obstruction after histamine challenge that was reversed after 2 weeks of antibiotics and intranasal flunisolide. Our 3 case reports demonstrate that infections can induce VCD. The key novel finding is that respiratory tract viral infections can induce or exacerbate VCD. We detected, by using

validated PCR techniques, the presence of either picornavirus (probably human rhinovirus), influenza A virus, or hMPV. To our knowledge, we have described the first cases of documented postviral VCD. The identification of hMPV is of importance. This recently discovered virus from the paramyxovirus family has a spectrum of disease ranging from mild respiratory symptoms to severe cough, wheeze, and pneumonia.⁹ VCD has not previously been described as a mode of presentation of hMPV infection and might account for a proportion of wheezing, cough, and dyspnea associated with this virus.

The pathophysiology of postviral paradoxical vocal cord adduction is poorly understood. Viruses infect the upper airway epithelium, causing a cytopathic effect, mucosal inflammation, and neural activation through nonadrenergic and noncholinergic nerve endings. The resulting sensory activation can lead to known reflex responses that include cough, bronchial hyperresponsiveness, and increased neutrophil recruitment.¹⁰ This manifests in the lower airways as postviral bronchial hyperresponsiveness and asthma exacerbation. It is tempting to postulate that postviral VCD might represent the consequence of epithelial damage and subsequent neural activation and inflammation in the larynx and the extrathoracic airways.

We also demonstrated in 2 cases that VCD can be completely reversible after recovery from an acute viral infection. These findings highlight the heterogeneity of VCD that can clinically present as a transitory response to a viral infection or as a recurrent illness.

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Loss of receptors and IgE *in vivo* during treatment with anti-IgE antibody

To the Editor:

How long does it take for IgE to be removed from mast cells and basophils, for example, under the influence of a therapeutic like omalizumab, and how does one interpret *in vivo* studies that address this question? *In vitro* studies of the dissociation of IgE from human basophils demonstrate a T_{1/2} of approximately 10 days.¹ This slow dissociation is unaltered by the presence of an IgE trap such as E25 (Omalizumab). Studies in last month's journal² examine the loss of receptor expression on tissue mast cells following treatment with Omalizumab, and these studies also suggest that dissociation of IgE is very slow. Indeed, on the basis of the *in vitro* studies, one would expect that significant loss of receptor from tissue mast cells would require many weeks. Ten half-lives—a typical rule-of-thumb length of time for a dissociative process—would be 100 days. Recent studies using Omalizumab and measuring functional changes *in vivo* indirectly suggest that loss of mast cell function is relatively slow.^{3,4} With these results in mind, the measurements of the loss of receptor on circulating basophils⁵ after treatment with Omalizumab—as noted in phase I trials—initially appear puzzling. These measurements showed a T_{1/2} of 3 days, considerably shorter than one would expect. However, a distinguishing characteristic between circulating basophils and tissue mast cells (or basophils in *in vitro* culture) is the brief transit time of basophils in circulation. The brief transit time may represent death or margination to tissues, but in either case, the cell is lost from observation. As a consequence, the apparent rapid loss of receptor expression (or cell surface IgE) is not the result of dissociation of IgE but the appearance of basophils in circulation that express less receptor. In essence, the plotted curve of receptor loss is a mirror reflection of the accumulation of receptor during maturation, or the apparent downregulation is really a reflection of the rate of upregulation.

The argument for this seemingly counterintuitive conclusion is as follows. Our previous studies have demonstrated that accumulation of FcεRI on the surface of basophils (and mast cells) results from IgE stabilizing the constitutive loading of receptor to the plasma membrane.⁶ In the absence of IgE, receptor that initially appears on the cell surface is rapidly lost. The loading of receptor on the