Confronting COVID-19-associated cough and the post-COVID syndrome: role of viral neurotropism, neuroinflammation, and neuroimmune responses

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Cough is one of the most common presenting symptoms of COVID-19, along with fever and loss of taste and smell. Cough can persist for weeks or months after SARS-CoV-2 infection, often accompanied by chronic fatigue, cognitive impairment, dyspnoea, or pain—a collection of long-term effects referred to as the post-COVID syndrome or long COVID. We hypothesise that the pathways of neurotropism, neuroinflammation, and neuroimmunomodulation through the vagal sensory nerves, which are implicated in SARS-CoV-2 infection, lead to a cough hypersensitivity state. The post-COVID syndrome might also result from neuroinflammatory events in the brain. We highlight gaps in understanding of the mechanisms of acute and chronic COVID-19-associated cough and post-COVID syndrome, consider potential ways to reduce the effect of COVID-19 by controlling cough, and suggest future directions for research and clinical practice. Although neuromodulators such as gabapentin or opioids might be considered for acute and chronic COVID-19 cough, we discuss the possible mechanisms of COVID-19-associated cough and the promise of new anti-inflammatories or neuromodulators that might successfully target both the cough of COVID-19 and the post-COVID syndrome.

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Introduction

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has had an unprecedented effect on global health since its discovery in Wuhan, China.[1,2] Even in countries where the first pandemic wave of the virus was controlled, second or third waves are happening or have been predicted to occur. With limited availability of effective vaccines, measures to reduce disease spread—such as physical distancing, wearing masks, and avoiding crowds—remain key strategies to combat the infection. Similar to the more common but less serious infections of the common cold or flu, cough is a key symptom of COVID-19 in the acute phase of the infection, and one that persists in the post-infective phase. Cough is not only distressing to patients, but also increases the risk of community transmission by respiratory droplets.[3] Stigmatisation of patients with cough can occur, leading to social isolation,[4] particularly during the COVID-19 pandemic. Identifying ways to control COVID-19-associated cough could help to prevent community transmission and disease spread, as well as removing the stigma of this symptom.

Evidence-based treatment options for COVID-19 cough are needed because patients with cough caused by common viral infections, including cold and flu, frequently resort to over-the-counter cough medicines. Patients with chronic cough also often seek antitussive therapies, but it is unknown whether such approaches are effective in post-COVID cough patients. We propose that it is important to consider cough as a target of intervention in the management of COVID-19 and post-COVID syndrome. However, we currently have little understanding of the mechanisms underlying COVID-19-associated cough. In this Personal View, we review the knowledge that has accumulated on cough in COVID-19, and discuss neuroinflammatory and neuroimmune mechanisms that could potentially underlie COVID-19-associated cough based on our understanding of the pathogenesis of COVID-19 and of the cough associated with other respiratory viruses. We

Key messages

- Acute COVID-19-associated cough with fever and a loss of taste and smell is common; chronic cough after SARS-CoV-2 infection occurs less frequently, but is common in the so-called post-COVID syndrome (long COVID), in which it is usually associated with other symptoms, including chronic fatigue, dyspnoea, chronic pain, and cognitive impairment (brain fog)
- Optimal management of COVID-19-associated cough remains unclear, although guidelines for current approaches to acute and chronic cough serve as reference
- COVID-19 cough might result from the invasion of vagal sensory neurons by SARS-CoV-2 or a neuroinflammatory response, or both, leading to peripheral and central hypersensitivity of cough pathways
- Studies are needed to provide data on the epidemiology and effect on quality of life of post-COVID chronic cough, together with insights into the cough hypersensitive state
- The hypothesis that the post-COVID syndrome results from a neuroinflammatory response affecting various regions of the brain to induce chronic fatigue, pain, dyspnoea, and cough should be addressed
- Although neuromodulators such as gabapentin or opioids might be considered for COVID-19 cough, new anti-inflammatories or neuromodulators could be considered to treat not only cough, but also the post-COVID syndrome; randomised studies are needed to examine the efficacy and safety of potential treatments during the acute and chronic phases of disease

	Unanswered questions	Potential research studies
Mechanistic studies		
Some sensory neurons (eg, those arising from the dorsal root ganglia) express entry factors for SARS-CoV-2, providing a route for neuronal infection; bronchopulmonary (vagal) sensory neuron terminals are in close apposition to airway epithelia and are probably exposed to SARS-CoV-2; bronchopulmonary (vagal) sensory neurons express innate viral recognition receptors and receptors for many cytokines	How does SARS-CoV-2 infection modify the activity of vagal sensory neurons mediating cough? What are the pathological consequences, within peripheral and central cough processing pathways, of SARS-CoV-2 infection? What is the inflammatory (neural and airway) profile of individuals with COVID-19-related cough? What is the impact of modulating neuroinflammation and neuroimmune processes on cough in COVID-19?	• Investigations of SARS-CoV-2 interaction with vagal bronchopulmonary sensory nerves, including neural expression of ACE2 and other entry factors, involvement of neural innate viral recognition factors, and role of resident and recruited airway and lung cells (and their mediators) in sensory neuronal activation. • Assessment of bronchopulmonary sensory neuron sensitivity in COVID-19, including use of animal models to evaluate cough response pathways and pathological changes following SARS-CoV-2 infection and treatment • Mechanistic studies in humans to assess peripheral and central processing to cough challenge with functional MRI, particularly with respect to post-COVID syndrome • Airway sampling to study inflammatory phenotype or effect of SARS-CoV-2 infection on airway nerve architecture or deformity
Acute COVID-19-related cough		
Cough is a key symptom of acute infection and an important mode of SARS-CoV-2 transmission	What are the characteristics of acute COVID-19-related cough? Can these characteristics aid diagnosis or prognosis? How does acute COVID-19-related cough respond to anti-inflammatory drugs (eg, corticosteroids) or SARS-CoV-2-targeted treatments? How does the presence of comorbid conditions or diagnoses influence the presence of COVID-19-related cough? Is antitussive therapy during the acute phase of COVID-19 safe and effective in treating morbidity or reducing SARS-CoV-2 transmission?	• Subjective and objective cough evaluation, with sound recording, and studies of relationship with health outcomes, with appropriate prospective comparator groups • Assessment of utility of cough sound analysis based on artificial intelligence algorithm to facilitate early detection of COVID-19 • Initial evaluation and re-evaluation of data from randomised clinical trials with cough documentation; future establishment of robust cough measures to monitor cough outcome and clinical responses • Randomised controlled trials of existing or emerging antitussive therapies with robust primary outcome measures in patients with COVID-19 and cough • Inclusion of validated cough endpoint measures in future viral inoculation models for optimisation of vaccine development
Chronic or post-COVID cough		
Cough persists in a subgroup of patients after resolution of acute disease; cough in post-COVID syndrome is usually associated with chronic fatigue and dyspnoea	What are the prevalence, longitudinal course, clinical features, and effect on quality of life of post-COVID cough? Are they similar to those encountered in cough hypersensitivity syndrome? Do treatments for cough hypersensitivity help in post-COVID cough management? Are novel treatments (eg, P2X3 antagonists) beneficial? Does cough modulation treatment (eg, speech pathology therapy) help? Should the treatment to post-COVID syndrome be a global approach to tackling all symptoms?	• Cross-sectional evaluation of prevalence of cough in those with co-existing pulmonary infiltrates, documented reflux, or history of airways disease, or in those taking ACE inhibitors; evaluation of changes with treatment response • Longitudinal follow-up and robust phenotyping with cough hypersensitivity testing (eg, cough challenge testing) and validated measures of cough (eg, cough-related quality of life); evaluation of sequelae and impact on quality of life (eg, incontinence and social exclusion) • Randomised controlled trials of novel cough therapies in patients with post-COVID cough using robust cough outcome measures (eg, ambulatory cough count); response of concomitant symptoms of post-COVID syndrome

ACE=angiotensin-converting enzyme. ACE2=angiotensin-converting enzyme 2. P2X3= P2X purinoceptor 3.

Table 2: **Future research in COVID-19-associated cough**

the UK National Institute for Health and Care Excellence guidelines for managing acute symptoms of COVID-19, only taking honey or opioid-derived antitussives are recommended for cough.[82] Opiates (such as codeine or low-dose morphine) could exert antitussive effects by acting on the cough reflex network in the brainstem,[83] and might have some effects in suppressing cough, particularly in the early stages. However, opiates are not universally effective and have associated risks of dependence, abuse, or central side-effects.[83]

Oral corticosteroids are often prescribed for acute lower respiratory tract infection and have been used by many centres to treat patients with post-COVID interstitial lung changes. Oral corticosteroids were no better than placebo in reducing cough duration in non-asthmatic adults with acute lower respiratory tract infection.[84] However, the situation with SARS-CoV-2 infection might be different, with the likely presence of an early inflammatory response and neuroimmune interactions underlying the acute cough. The report that dexamethasone reduces the mortality rate of hospital-treated patients with COVID-19 provides some support for the use of corticosteroids.[85,86] However, cough was not assessed in these trials,[85,86] nor was it measured in any other trials of therapies for COVID-19, such as the study of the antiviral replicating agent remdesivir.[87] Cough measurements should be incorporated into future trials.