Asia Pac Allergy. 2022 Apr;12(2):e19
https://doi.org/10.5415/apallergy.2022.12.e19
pISSN 2233-8276·eISSN 2233-8268

Asia Pacific allergy

Case Report

Long-COVID severe refractory cough: discussion of a case with 6-week longitudinal cough characterization

Yu Ri Kang [1], **Ji-Yoon Oh** [1], **Ji-Hyang Lee** [1], **Peter M. Small** [2], **Kian Fan Chung** [3], **and Woo-Jung Song** [1,*]

[1]Department of Allergy and Clinical Immunology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[2]Hyfe, Inc and University of Washington, Department of Global Health, Seattle, WA, USA
[3]National Heart and Lung Institute, Imperial College London, London, UK

Received: Apr 22, 2022
Accepted: Apr 22, 2022
Published online: Apr 25, 2022

***Correspondence to**
Woo-Jung Song
Department of Allergy and Clinical Immunology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
Tel: +82-2-3010-3288
Email: swj0126@amc.seoul.kr

ORCID iDs
Yu Ri Kang
https://orcid.org/0000-0001-5749-2040
Ji-Yoon Oh
https://orcid.org/0000-0002-2339-7878
Ji-Hyang Lee
https://orcid.org/0000-0003-4286-3114
Peter M. Small
https://orcid.org/0000-0001-5403-8985
Kian Fan Chung
https://orcid.org/0000-0001-7101-1426
Woo-Jung Song
https://orcid.org/0000-0002-4630-9922

Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Long coronavirus disease (COVID) refers to an array of variable and fluctuating symptoms experienced after acute illness, with signs and symptoms that persist for 8–12 weeks and are not otherwise explicable. Cough is the most common symptom of acute COVID-19, but cough may persist in some individuals for weeks or months after recovery from acute phase. Long-COVID cough patients may get stigmatised because of the public fear of contagion and reinfection. However, clinical characteristics and longitudinal course of long-COVID cough have not been reported in detail, and evidence-based treatment is also lacking. In this paper, we describe a case of long-COVID severe refractory cough with features of laryngeal hypersensitivity and dysfunction. We characterized cough using patient-reported outcomes and engaged in continuous cough frequency monitoring. Through the case study, we discuss potential mechanisms, managements, and clinical implications of long-COVID refractory cough problems.

Keywords: Cough; Coronavirus; Hypersensitivity

INTRODUCTION

Cough is the most common symptom of acute coronavirus disease-19 (COVID-19), but cough may persist in 10%–20% of the patients for weeks or months after recovery from acute phase [1]. Long COVID (post-COVID syndrome) refers to an array of variable and fluctuating symptoms experienced after acute illness, with signs and symptoms that persist for 8–12 weeks and are not otherwise explicable [2]. Cough is a frequent symptom of long COVID [1, 3]; such patients may get stigmatised because of the public fear of contagion and reinfection [4]. Cough may thus limit social activity and impair quality of life seriously.

Despite the substantial impacts, the clinical characteristics and longitudinal course of long-COVID cough have not been reported in detail, and evidence-based treatment is also lacking. Here, we describe a case of long-COVID severe refractory cough. In diagnostic evaluations, he exhibited features of laryngeal hypersensitivity and dysfunction. For cough characterization, we recorded cough patient-reported outcomes (PROs) and engaged in continuous cough frequency monitoring for 6 weeks of treatments. Through the case study,

Author Contributions

Conceptualization: Woo-Jung Song, Peter M. Small, Kian Fan Chung. Formal analysis: Yu Ri Kang, Woo-Jung Song. Investigation: Yu Ri Kang, Woo-Jung Song. Methodology: Yu Ri Kang, Ji-Yoon Oh, Ji-Hyang Lee, Woo-Jung Song. Project administration: Yu Ri Kang. Writing - original draft: Yu Ri Kang, Woo-Jung Song. Writing - review & editing: Ji-Yoon Oh, Ji-Hyang Lee, Peter M. Small, Kian Fan Chung.

we discuss potential mechanisms, managements, and clinical implications of long-COVID cough problems.

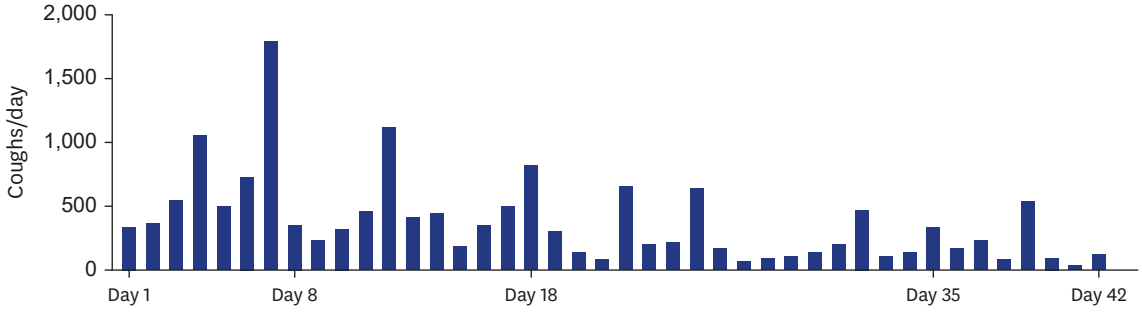
CASE REPORT

Baseline description

A 40-year-old man was referred to our cough clinic with persistent cough. He was a former smoker but had no previous history of chronic allergic or respiratory illness. He had suffered from severe COVID-19 pneumonia 4 months prior, requiring 1 month of hospitalisation and intensive care. At discharge, he exhibited a cough, blood-tinged sputum, dyspnea, and chest pain; however, the symptoms other than cough and dyspnea gradually resolved over time. When he visited our clinic, he was suffering from daily cough and intermittent breathlessness that had persisted for 3 months after discharge. The cough was mainly dry but was intermittently accompanied by a small amount of phlegm. The cough was severe during daytime, triggered or worsened by cold or dry air, motion, talking, eating, or deep breathing, but also occurred during sleep. He reported throat discomfort, and an urge-to-cough sensation. He had no symptoms suggesting asthma, a nasal disease, or gastroesophageal acid reflux. His cough severity numerical rating scale score was 9 (0–10; a higher score indicates a more severe cough) at baseline (day 1; **Fig. 1**). The Cough Hypersensitivity Questionnaire (CHQ) score was 16 (0–22; a higher score indicates more cough triggers and greater laryngeal sensation) [5], and the Leicester Cough Questionnaire (LCQ) score was 5.6 (3–21; a lower score indicates a higher impact of cough on the quality of life) [6]. That impact was profound in the social domain (LCQ social domain score: 1.0). The Medical Research Council (MRC) breathlessness scale score was 3.

Diagnostic investigations

On examination, the patient was alert and orientated. Physical examination of the respiratory, cardiovascular, and gastrointestinal systems was unremarkable. Chest computed tomography revealed no evidence of a residual lesion or lung fibrosis. The spirometric findings were within the normal ranges: forced expiratory volume in 1 second



Cough severity (0–10)	9 7 7 9 6 7 9 9		7 5 3 3 7 4 4 8 2 2 2 3 3 3 8 2 5 4 2 3 2 7 2 1 3	
LCQ total (3–21)	5.6	7.7	8.9	7.1
Physical	2.6	3.1	3.3	2.9
Psychological	2.0	2.9	3.1	2.7
Social	1.0	1.7	2.5	1.5
CHQ total (0–23)	16	NA	14	19

Fig. 1. Longitudinal changes in the daily objective cough frequency and subjective cough scores over 6 weeks of treatment. LCQ, Leicester Cough Questionnaire; CHQ, Cough Hypersensitivity Questionnaire; NA, not available.

https://doi.org/10.5415/apallergy.2022.12.e19

Asia Pacific allergy

(FEV_1) 93% of predicted, forced vital capacity (FVC) 83% of predicted, and FEV_1/FVC 89%. Fractional exhaled nitric oxide test could not be performed due to the difficulty to maintain constant expiration. Blood tests, including a complete blood count, blood chemistry, and a coagulation panel, were unremarkable. Sputum microbiology, including acid-fast bacillus staining, was negative.

Treatments and follow-up

His cough was not accompanied by any evident pathologic diseases and had been unresponsive to first-generation antihistamines, codeine, and inhaled corticosteroids. As he was seriously troubled by coughing and experienced ineffective treatments for 3 months, we decided to commence high-intensity treatments including cough neuromodulators (gabapentin 100 mg twice a day [bid] and amitriptyline 10 mg once a day), azithromycin 250 mg every other day, and prednisolone 15 mg bid. A low-dose proton pump inhibitor was given for a gastroprotective purpose. He was also educated to try cough suppression techniques and improve vocal hygiene [7-9]. We started continuous cough monitoring using the Hyfe, a smartphone application-based cough tracker [10].

On day 8, challenge laryngoscopy was performed. No structural abnormality was found, but grade 1 glottic adduction and grade 2 supraglottic constriction [11] were observed during effort inspiration, indicating a comorbid mild-to-moderate laryngeal dysfunction (**Fig. 2**). Notably, he felt the relief from strong urge-to-cough sensation during the flexible laryngoscope was placed in the throat. The continuous cough monitoring revealed daily cough counts of about 500/day during the first week. The maximum daily cough count was 1,793 (on day 4; **Fig. 1**); his cough was particularly worsened by talking, motion, or physical activity. Based on the laryngeal hypersensitivity and dysfunction (high CHQ score and positive findings on challenge laryngoscopy), gabapentin was increased to 300 mg bid, while other drugs were gradually tapered.

On day 18, he still suffered from coughing, intermittently aggravated by physical stimuli such as exercise and talking, but the PRO measurements and objective cough counts revealed gradual reductions in cough severity scores and objective cough frequency. He experienced fatigue after the increased gabapentin dosing, but this was relatively well tolerated; the

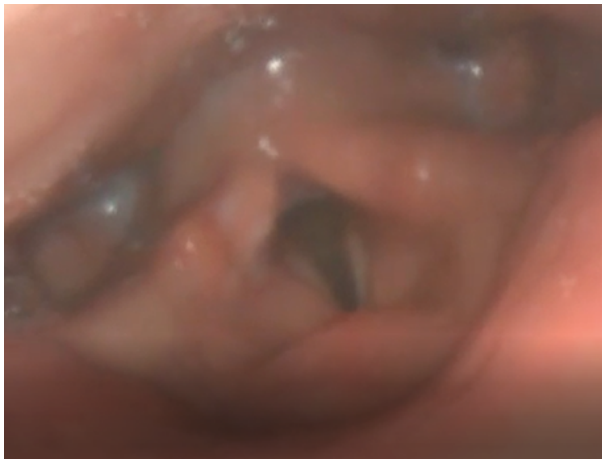


Fig. 2. Challenge laryngoscopy revealed mild-to-moderate laryngeal dysfunction. Grade 1 glottic adduction and grade 2 supraglottic constriction [11] were observed during effortful inspiration. This might explain his dyspnoea triggered by breathing, talking, or physical exercise.

https://doi.org/10.5415/apallergy.2022.12.e19

gabapentin dose was further increased to 300 mg 3 times a day. On day 35, further reductions in the objective cough frequency and subjective cough severity score were observed, but the LCQ and CHQ scores had not improved. Particularly, the LCQ social domain score was aggravated (1.5). The MRC breathlessness scale score was 2. He experienced severe fatigue, eyelid twitching, and peripheral tingling pain, and thus we decided to decrease the dose of gabapentin to 100 mg bid, and after 1 week, we observed that his cough was not aggravated (**Fig. 1**). We will continue to follow him up until his cough is resolved.

This case report was approved by the Institutional Review Board (IRB) of the Asan Medical Center (IRB No. 2022-0524). The presented data is a part of the Korean Chronic Cough registry, a prospective, observational cohort study (IRB No. 2019-0754). The patient agreed to participate in the prospective follow-up and case reporting. An informed consent was obtained.

DISCUSSION

In this paper, we described the case of a young man with long-COVID severe refractory cough. Although he remains under follow-up, we consider that an interim report may help to increase public and medical awareness of this refractory condition. We draw no generalisation but suggest that (1) post-COVID cough can be severe, persistent, and treatment-refractory in some patients; and (2) that the cough can be accompanied by laryngeal hypersensitivity and dysfunction. The LCQ data showed that the impact of long-COVID cough on quality of life may be substantial, especially in the social domain.

Neither the cough nor the breathlessness was explicable on spirometry or chest imaging, and therapies targeting asthma and upper airway disease, were ineffective. However, laryngeal hypersensitivity and dysfunction were evident, as revealed by a high CHQ score and positive findings on challenge laryngoscopy. Laryngeal hypersensitivity/dysfunction are common in patients with chronic cough, particularly refractory cough [5, 12]. We thus suggest that functional aberrations of the larynx underlie the persistent cough and breathlessness in this case. Also, his urge-to-cough sensation was greatly relieved while the flexible laryngoscope was placed *in situ* (transiently causing pain and physical discomfort), suggesting neural gating mechanisms involved in his cough.

Although we observed that cough gradually improved with cough neuromodulators, we presume that the observed improvement may be attributable to regression to the mean effects or to benefits from behavioural cough suppression techniques and vocal hygiene, because his cough remained relatively stable after dose de-escalation of gabapentin (at day 35). This represents only a single case, and treatments for long-COVID cough should be investigated in controlled trials.

There is no consensus on the management of long-COVID cough patients. The clinical practice guidelines for chronic cough should perhaps be followed [1, 7-9]. However, as the clinical presentations and symptoms of long COVID are variable [1, 13], the approach should be individualised. Comorbidities that may potentially cause dyspnoea should be actively evaluated. Drugs such as gabapentin or amitriptyline may cause fatigue or compromise cognitive function [8]. Studies with more patients are required, followed by clinical trials. Novel antitussive drugs including P2X3 antagonists [14] might be trailed in severe refractory cough cases.

https://doi.org/10.5415/apallergy.2022.12.e19

We found different utility of PROs and objective cough frequency in evaluating longitudinal changes of his cough status. The PROs, such as LCQ and CHQ, were helpful to understand the impact on quality of life, particularly in the social domain, and the hypersensitive nature of the cough. We utilized continuous cough frequency monitoring and found that it was more sensitive in evaluating cough variability and responses to the treatments in a short term. This gap between LCQ and cough frequency might be due to longer time scale of the PROs, but also indicate that the impact of long-COVID cough on quality of life persists longer than coughing itself.

Finally, we highlight the impact of cough in long-COVID patients. As shown in this case, the impact can be substantial particularly in the social aspect of life. As suggested in 6-month or longer prospective follow-up studies of post-COVID patients [15-17], physical symptoms including anosmia, chest tightness, or cough may improve over time, but psychological and social issues may persist for longer periods of time. Job loss is another frequent complication [16, 18].

We hypothesize that active intervention to control midterm health issues (2–6 months) including cough will help to prevent or reduce long-term (>6–12 months) consequences in patients with long COVID, such as anxiety, depression, social isolation, or job loss. As uncertainty seems to trigger a vicious cycle of long COVID [18, 19], objective tests should seek to identify any pathology of cough that requires treatment and reduce health concerns. It is also important to raise public awareness of the condition.

In conclusion, we report a case of long-COVID refractory cough comorbid with laryngeal dysfunction and hypersensitivity; we characterized the nature and longitudinal changes of cough using the PROs and continuous cough frequency monitoring for 6 weeks. Prospective cohort studies are warranted to understand the clinical characteristics of and identify optimal managements for patients with long-COVID refractory cough.

ACKNOWLEDGEMENTS

The work was supported in part by a research grant from Investigator-Initiated Studies Program of Merck Sharp & Dohme Corp.. The opinions expressed in this paper are those of the authors and do not necessarily represent those of Merck Sharp & Dohme Corp.

REFERENCES

1. Song WJ, Hui CKM, Hull JH, Birring SS, McGarvey L, Mazzone SB, Chung KF. Confronting COVID-19-associated cough and the post-COVID syndrome: role of viral neurotropism, neuroinflammation, and neuroimmune responses. Lancet Respir Med 2021;9:533-44.
PUBMED | CROSSREF
2. Crook H, Raza S, Nowell J, Young M, Edison P. Long covid-mechanisms, risk factors, and management. BMJ 2021;374:n1648.
PUBMED | CROSSREF
3. Carfì A, Bernabei R, Landi F; Gemelli Against C-P-ACSG. Persistent symptoms in patients after acute COVID-19. JAMA 2020;324:603-5.
PUBMED | CROSSREF
4. Won HK, Song WJ. Impact and disease burden of chronic cough. Asia Pac Allergy 2021;11:e22.
PUBMED | CROSSREF

5. Won HK, Kang SY, Kang Y, An J, Lee JH, Lee SM, Kwon JW, Kim MH, Jo EJ, Lee SE, Kim SH, Kim SH, Chang YS, Kim SH, Lee BJ, Cho SH, Birring SS, Song WJ. Cough-related laryngeal sensations and triggers in adults with chronic cough: symptom profile and impact. Allergy Asthma Immunol Res 2019;11:622-31.
PUBMED | CROSSREF

6. Kwon JW, Moon JY, Kim SH, Song WJ, Kim MH, Kang MG, Lim KH, Lee SH, Lee SM, Lee JY, Kwon HS, Kim KM, Kim SH, Kim SH, Jeong JW, Kim CW, Cho SH, Lee BJ; Work Group for Chronic Cough tKAoAA, Clinical I. Reliability and validity of a Korean version of the leicester cough questionnaire. Allergy Asthma Immunol Res 2015;7:230-3.
PUBMED | CROSSREF

7. Gibson P, Wang G, McGarvey L, Vertigan AE, Altman KW, Birring SS, Panel CEC. Treatment of unexplained chronic cough: CHEST guideline and expert panel report. Chest 2016;149:27-44.
PUBMED | CROSSREF

8. Morice AH, Millqvist E, Bieksiene K, Birring SS, Dicpinigaitis P, Domingo Ribas C, Hilton Boon M, Kantar A, Lai K, McGarvey L, Rigau D, Satia I, Smith J, Song WJ, Tonia T, van den Berg JWK, van Manen MJG, Zacharasiewicz A. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Eur Respir J 2020;55:1901136.
PUBMED | CROSSREF

9. Song DJ, Song WJ, Kwon JW, Kim GW, Kim MA, Kim MY, Kim MH, Kim SH, Kim SH, Kim SH, Kim ST, Kim SH, Kim JK, Kim JH, Kim HJ, Kim HB, Park KH, Yoon JK, Lee BJ, Lee SE, Lee YM, Lee YJ, Lim KH, Jeon YH, Jo EJ, Jee YK, Jin HJ, Choi SH, Hur GY, Cho SH, Kim SH, Lim DH. KAAACI evidence-based clinical practice guidelines for chronic cough in adults and children in Korea. Allergy Asthma Immunol Res 2018;10:591-613.
PUBMED | CROSSREF

10. Gabaldón-Figueira JC, Keen E, Rudd M, Orrilo V, Blavia I, Chaccour J, Galvosas M, Small P, Lapierre SG, Chaccour C. Longitudinal passive cough monitoring and its implications for detecting changes in clinical status. ERJ Open Res Forthcoming 2022.
CROSSREF

11. Maat RC, Røksund OD, Halvorsen T, Skadberg BT, Olofsson J, Ellingsen TA, Aarstad HJ, Heimdal JH. Audiovisual assessment of exercise-induced laryngeal obstruction: reliability and validity of observations. Eur Arch Otorhinolaryngol 2009;266:1929-36.
PUBMED | CROSSREF

12. Vertigan AE, Kapela SM, Kearney EK, Gibson PG. Laryngeal dysfunction in cough hypersensitivity syndrome: a cross-sectional observational study. J Allergy Clin Immunol Pract 2018;6:2087-95.
PUBMED | CROSSREF

13. Lorent N, Vande Weygaerde Y, Claeys E, Guler Caamano Fajardo I, De Vos N, De Wever W, Salhi B, Gyselinck I, Bosteels C, Lambrecht BN, Everaerts S, Verschraegen S, Schepers C, Demeyer H, Heyns A, Depuydt P, Oeyen S, Van Bleyenbergh P, Godinas L, Dupont L, Hermans G, Derom E, Gosselink R, Janssens W, Van Braeckel E. Prospective longitudinal evaluation of hospitalised COVID-19 survivors 3 and 12 months after discharge. ERJ Open Res 2022;8:00004-02022.
PUBMED | CROSSREF

14. McGarvey LP, Birring SS, Morice AH, Dicpinigaitis PV, Pavord ID, Schelfhout J, Nguyen AM, Li Q, Tzontcheva A, Iskold B, Green SA, Rosa C, Muccino DR, Smith JA, Smith JA; COUGH-1 and COUGH-2 Investigators. Efficacy and safety of gefapixant, a $P2X_3$ receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. Lancet 2022;399:909-23.
PUBMED | CROSSREF

15. Tran VT, Porcher R, Pane I, Ravaud P. Course of post COVID-19 disease symptoms over time in the ComPaRe long COVID prospective e-cohort. Nat Commun 2022;13:1812.
PUBMED | CROSSREF

16. Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, Hu P, Guo L, Liu M, Xu J, Zhang X, Qu Y, Fan Y, Li X, Li C, Yu T, Xia J, Wei M, Chen L, Li Y, Xiao F, Liu D, Wang J, Wang X, Cao B. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet 2021;398:747-58.
PUBMED | CROSSREF

17. Kim Y, Bitna-Ha , Kim SW, Chang HH, Kwon KT, Bae S, Hwang S. Post-acute COVID-19 syndrome in patients after 12 months from COVID-19 infection in Korea. BMC Infect Dis 2022;22:93.
PUBMED | CROSSREF

18. Buttery S, Philip KEJ, Williams P, Fallas A, West B, Cumella A, Cheung C, Walker S, Quint JK, Polkey MI, Hopkinson NS. Patient symptoms and experience following COVID-19: results from a UK-wide survey. BMJ Open Respir Res 2021;8:e001075.
PUBMED | CROSSREF

19. Taribagil P, Creer D, Tahir H. 'Long COVID' syndrome. BMJ Case Reports CP 2021;14:e241485.
PUBMED | CROSSREF