Case Report

Post-acute COVID-19- Related Cough Syncope: A Case Report from Saudi Arabia

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Abstract

A 41-year-old male unvaccinated for COVID-19 presented to the emergency department with syncope due to a severe cough, 2 weeks after recovering from COVID-19 for the second time. He demonstrated symptoms of wheezing during the physical exam. However, vitals, lab findings, and the chest CT scan were normal. He was started on proton-pump inhibitors, inhaled antimuscarinic and gabapentin drugs for 7 days on top of a short course of antibiotics, and oral as well as inhaled steroids. His syncopial cough episodes have subsided completely and remain stable. Therefore, clinicians should be aware of the uncommon complication of COVID-19 in the post-acute phase of the disease. Possible predictive factors for syncopal cough are young age, history of COVID-19 infection, as he has been infected twice, and not receiving a COVID-19 vaccine. Gabapentin and antimuscarinic agents may play roles in managing COVID-19-related cough syncope and should be used as part of a multimodal intervention that targets cough, mainly to shorten cough syncope episodes in surviving patients.

Keywords: Syncope, Cough, Post-acute, Adults, Gabapentin, Antimuscarinic agents

Introduction

Around December 2019, the first cases of the *coronavirus* (COVID-19) infections were reported in China: secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) novel virus [1, 2]. The World Health Organization (WHO) has tracked 768,237,788 confirmed cases and 6,951,677 deaths globally. Saudi Arabia has had about 841,469 confirmed cases, with a fatality rate of 1.15% [3]. The COVID-19 virus mainly attacks the respiratory system. However, the virus has negatively affected other systems, such as the cardiovascular, hematopoietic, and nervous systems [4]. Herein, we describe the first case of post-acute COVID-19 cough syncope in adults, globally and locally.

Case Presentation

A 40-year-old man who works in a health care facility and unvaccinated against COVID-19 infection (weight 121 kg, height 5.9 ft) with a past medical history of controlled seasonal asthma (on budesonide inhaler, 2 puffs twice per day and tiotropium bromide inhaler, 2 puffs once per day) and no known drug allergy was admitted to the hospital with cough syncope while driving and shortness of breath 2 weeks post-COVID-19 infection for the second time. The syncopal episodes were short and happened while he was severely coughing about 4 times; the last two episodes occurred while he was driving. Vitals upon admission were as follows: blood pressure (BP): 123/70 mmHg, heart rate (HR): 96 beats per minute (BPM), respiratory rate (RR): 18 (breaths per minute) BPM, temperature: 36.7 C, SPO^2: 100%, pain score: 2/10. The calculated COVID-19 exposure risk upon admission was 13. The patient had chest bilateral wheezing upon physical exam. A chest X-ray was positive for bronchitis; chest CT showed no evidence of ground-glass haze, consolidation, collapse, or pleural effusion. Echocardiogram was normal, bilateral lower limb venous doppler was normal, and all other lab findings were within normal range except for lymphocytes % which were 54.9 (reference 20-24), D-dimer was 1.09 (reference 0.0-0.5 FEU µg/mL). Medications upon hospitalization were ceftriaxone 2 gm intravenously (IV) daily for 3 days, levofloxacin 500 mg IV daily for 3 days, esomeprazole IV 40 mg daily, solumedrol 40 mg IV daily, enoxaparin 40 mg subcutaneous daily and gabapentin 300 mg daily. His status and vitals were stable during the admission course (BP: 105/66-126/67 mmHg, HR: 70-90 BPM, RR: 20 BPM, SPO^2: 95-97%), and syncopial episodes subsided. Accordingly, he was discharged after 3 days, having been prescribed azithromycin 500 mg orally once daily for 3 days, ipratropium bromide 0.5 mg via nebulizer 3 times per day for 1 week, budesonide 0.5 mg via nebulizer 3 times per day for

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1 week, pantoprazole 40 mg orally daily for 1 week, prednisolone 25 mg orally daily for 5 days, and gabapentin 300 mg daily before sleep for 7 days. He returned for a follow-up appointment and has been stable.

Results and Discussion

This report shows a patient with cough syncope, 14 days after developing a COVID-19 infection for the second time. This will add to the existing body of literature and help better understand the course of the COVID-19 infection in the post-acute phase of the disease and, most importantly, identify patients at risk for cough syncope to isolate them at earlier stages.

Syncope is a transient loss of consciousness due to cerebral hypoperfusion. A syncopal episode usually onsets rapidly, short with a complete recovery. Presyncope, on the other hand, is the state of a prodromal syncope without the actual loss of consciousness [5]. COVID-19-associated syncope has been reported in the literature as one of the possible symptoms of a COVID-19 infection that may develop at the beginning of or during the infection, or even a couple of days before patients test positive for COVID-19 (an average of 3.16 ± 1.40 days prior) [1, 6]. In the early phases of the COVID-19 pandemic, a low prevalence of syncope was reported in the literature (range: 3–7%). However, in 2020, about 24% of COVID-19-infected patients (*N*: 102) went to healthcare facilities with syncope or presyncope episodes as their initial symptoms. Syncope in COVID-19-infected patients might be more prevalent than what has been reported so far. COVID-19-associated syncope or presyncope cases were mainly reported in the US, Canada, Australia, China, Austria, Hungary, Portugal, Italy, Turkey, Switzerland, Tunisia, France, Egypt, Israel, and Ukraine [1, 7]. Two studies reported syncope with a COVID-19 infection 3–4 weeks after being cleared due to postural orthostatic tachycardia syndrome [8, 9]. Males have reported it more frequently (61.2%) [1], and thus gender could be a risk factor.

Syncope in the acute phase of COVID-19 infection due to unknown causes was reported in 87.9% (531/604) of cases. The remaining cases involved reflex syncope, syncope due to orthostatic hypotension, and presumable cardiac syncope [10]. Comorbidities that were reported in those cases included arterial hypertension, diabetes mellitus, obesity, dyslipidemia, and heart disease [10]. Those aged 18–44 did not show signs of syncope [11]. Laboratory findings showed abnormalities in COVID-19-infected patients with syncope, including high C-reactive protein, high D-dimer, high troponin, and lymphocytopenia. Additionally, syncope episodes were significantly higher in patients using beta blockers [10]. Some COVID-19-infected patients had lower blood pressure and heart rates at admission during the acute phase of the infection, with no established correlation with COVID-19 severity [12]. Canetta *et al*. reported that about 35 COVID-19-infected patients developed syncope as a primary symptom of the infection, and patients who suffered syncope had lower heart rates compared to infected patients with no syncope. However, these patients were febrile, which could contribute to bradycardia [13]. Additional findings show lower heart rates in COVID-19-infected patients who suffered syncope compared to non-syncopal COVID-19-infected patients when they were matched for temperature [6].

The main causes of syncope in general include reflex (vasovagal or situational, such as in the case of cough or defection), neurogenic (primary or secondary autonomic failure), cardiac (arrhythmic or structural conditions), endocrine (pheochromocytoma, mastocytosis, or vasoactive intestinal peptide tumor), medication, or infection (such as Chagas disease or Lyme disease). COVID-19 infection may affect the autonomic nervous system. Note that the most common pattern of syncope that was reported in the literature was unexplained syncope, followed by reflex and orthostatic hypotension [14].

Cough syncope on the other hand (also called laryngeal ictus) is "a syndrome that is characterized by cough and the loss of consciousness that occurs in seconds and followed by a quick recovery." Generally, it occurs in young adults or men with a history of obstructive lung diseases. It is believed to be due to an increase in the intrathoracic pressure secondary to the coughing that leads to a reduction in the venous return and cardiac output, thus reducing cerebral perfusion and loss of consciousness [15].

However, this was not the case with our patient, as he developed syncope as a secondary to severe coughing after being diagnosed with COVID-19 for the second time, 14 days after the official diagnosis. COVID-19-related syncope by itself has been reported in patients older than 85 years, but our patient was in his early 40s. Also, the reported cases in the literature discussed syncope alone as a possible early manifestation of a COVID-19 infection [1], whereas our patient suffered from a severe cough that resulted in life-threatening syncopal episodes. Additionally, some medications known to cause syncope include tricyclic antidepressants, alpha1-antagonists, diuretics, and nitrates, among others [14]. Nevertheless, our patient was free of medications except for a budesonide inhaler (2 puffs twice per day) and a tiotropium bromide inhaler (2 puffs once per day for asthma), which he had not been used for a while due to his asthma stability; hence, his syncopal episodes were not triggered by medication use.

The target of interventions in this case was to control the cough because it was the primary cause of the syncope. Thus, the medical team started the patient on proton-pump inhibitors and gabapentin for 7 days on top of a short course of antibiotics and oral as well as inhaled steroids. The gabapentin, which is a neuromodulator, was initiated at a dose of 300 mg daily, to lessen the cough hypersensitivity, as it has been hypothesized that SARS-CoV-2 may impact the sensory nerves, resulting in neuroinflammation and neuroimmune

interactions, which could be the central cause of the cough hypersensitivity. Some evidence supports gabapentin's use in refractory chronic cough in non-COVID-19 infected patients [16, 17]. Also, antimuscarinic drugs could help manage a post-acute COVID-19 cough by reducing cough hypersensitivity secondary to viral respiratory infections [18]. Thus, we initiated ipratropium in this patient. Moreover, a previously reported case described a healthy 42-year-old patient who suffered from multiple episodes of cough syncope and was initiated on a proton pump inhibitor (PPI) for a week due to symptoms suggestive of pyrosis. After implementing treatment, his cough and syncopal episodes were terminated [15].

Early identification of patients at risk and early management would help lessen the burden of a post-acute COVID-19-related cough, which can last for months and impact one's quality of life. Some predictive factors of chronic cough in post-acute COVID-19 reported in the literature were female gender, the presence of underlying respiratory diseases, and the severity of the acute phase of the infection [19]. However, other possible predictive factors from our case are young age, history of repeated COVID-19 infection, as he has been infected twice, and not receiving a COVID-19 vaccine.

Even though the WHO has downgraded the status of the COVID-19 pandemic, it has not finished. Post-acute COVID-19-related cough has to be taken seriously. The existing protocol to manage COVID-19-infected patients in Saudi Arabia includes generating online sick leaves for 7 days sent to the infected patient through their mobile and a red flag appearing on the page of a governmental application that they were required to download during the pandemic. After this process, COVID-19 survivors report back on the 8th day with no follow-up. Thus, it is important to adjust the protocol that deals with this virus or any respiratory viruses in the future to include automatic follow-up for patients who present with certain detrimental symptoms or suggestive risk factors after the acute phase of the infection, such as persisting cough, syncope, or preexisting lung disease.

Conclusion

Cough syncope is an uncommon complication of COVID-19 infection. The main etiology of COVID-19-associated cough remains unknown in most cases. Our case of cough syncope is the first locally and globally. It sheds some light on and adds to the current body of evidence about the long-term consequences of COVID-19 infection. The management is unclear. However, gabapentin and antimuscarinic agents may play roles in managing post-acute COVID-19-related cough syncope and should be used as part of a multimodal intervention that targets cough, mainly to shorten cough syncopal episodes in surviving patients. More research is needed to point healthcare providers to evidence-based therapies that target chronic cough in COVID-19 survivors and to understand their roles in mitigating cough at earlier stages to lessen its impact on survivors' quality of life.

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