Syncope as the presenting symptom of COVID-19 infection

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Introduction
The severity of COVID-19 symptoms can range from none to very mild or severe. They usually appear 2 to 14 days after virus exposure and can include fever, cough, shortness of breath, headache, diarrhea, vomiting, runny nose, sore throat, anosmia and ageusia, conjunctivitis, tiredness, and aches.\(^1\) To our knowledge, syncope alone has not been described as a symptom associated with COVID-19 infection. We report a case series of syncope as the presenting symptom in otherwise asymptomatic patients with COVID-19 infection.

Case report
Case 1
A 71-year-old man with hypertension and coronary artery disease, status post permanent pacemaker (PPM) implantation 3 years before, presented to the Emergency Department (ED) with a presyncopal episode while sitting. He reported lightheadedness, profuse sweating, and blurred vision. In the ED his blood pressure was 115/75 mm Hg, heart rate 75 beats per minute, and oxygen saturation 98% on room air. His device was interrogated and showed normal functioning, regular parameters, and no arrhythmias. In order to be admitted on a regular medicine floor he was tested for COVID-19 infection. His nasopharyngeal swab result was positive. His chest radiograph was unremarkable (Figure 1A). He was placed on isolation precautions and after 4 days he developed a fever; subsequently, right lobe pneumonia was diagnosed on chest radiograph (Figure 1B).

Case 2
A 65-year-old woman with history of mitral valve stenosis, status post valve replacement with a bioprosthesis 13 years before, PPM implanted for advanced atrioventricular (AV) block at the time of cardiac surgery, and history of atrial fibrillation (AF) had a traumatic syncope preceded by lightheadedness. She did not seek medical attention at the time of syncope. In the ED his blood pressure was 115/75 mm Hg, heart rate 75 beats per minute, and oxygen saturation 98% on room air. His device was interrogated and showed normal functioning, regular parameters, and no arrhythmias. In order to be admitted on a regular medicine floor he was tested for COVID-19 infection. His nasopharyngeal swab result was positive. His chest radiograph was unremarkable (Figure 1A). He was placed on isolation precautions and after 4 days he developed a fever; subsequently, right lobe pneumonia was diagnosed on chest radiograph (Figure 1B).

Case 3
A 79-year-old man with history of hypertension, diabetes mellitus, and transient ischemic attack was admitted for traumatic syncope without any prodromes. He had a cardiac loop recorder previously implanted to search for silent AF, which showed paroxysmal third-degree AV block at the time of the clinical event. In order to be admitted for PPM implantation he was tested for COVID-19 infection. The nucleic acid–based polymerase chain reaction did not show any presence of the virus and the patient underwent uncomplicated implantation of a dual-chamber PPM. The following day the patient had 2 presyncopal episodes while lying down, with profuse sweating, lightheadedness, and nausea, recognized by the patient as different from the symptom that led to PPM implantation.

KEY TEACHING POINTS
- Syncope alone has never been described as a symptom associated with COVID-19 infection.
- Whether the exact mechanism is still debated, recognizing this possibility is of utmost importance for undertaking appropriate isolation precaution.
- Its early recognition might help COVID-19 treatment, fighting the infection at its initial phase.

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implantation. TTE and chest radiograph were normal. Two days later, he developed a mild fever (100.2°F). New nasopharyngeal and throat swabs were performed and results were positive for COVID-19 virus.

Case 4
A 75-year-old man with history of Chagas disease, status post PPM implantation 7 years before owing to advanced AV block and subsequent device upgrade to implantable cardioverter-defibrillator (ICD) because of sustained ventricular tachycardia, was hospitalized because of COVID-19 pneumonia (Figure 2A). He was treated according to the therapeutic protocol in force at that time (hydroxychloroquine and lopinavir/ritonavir). After 20 days he was deemed recovered from COVID-19 disease following 2 negative swabs 48 hours apart and was discharged home (Figure 2B). Five days later, he presented again to the ED because of a syncope preceded by dizziness. His ICD was interrogated and showed normal functioning, regular parameters, and no arrhythmias. An angiographic CT scan of the chest ruled out pulmonary embolism. Nasopharyngeal and throat swabs were repeated and results were positive for COVID-19 virus.

Case 5
A 75-year-old man with history of dilated cardiomyopathy, status post PPM implantation 12 years before, was admitted for heart failure exacerbation. His symptoms improved after appropriate treatment with intravenous diuretics. He tested negative for COVID-19 infection. Because of reduced left ventricular ejection fraction despite optimal medical therapy, he underwent device upgrade to an ICD. During the procedure he developed an intense vagal reaction with drop in blood pressure to 60/40 mm Hg with presyncope and diaphoresis, which resolved after fluid challenge. TTE ruled out pericardial effusion. Chest radiograph was within normal limits (Figure 3A). He was discharged home asymptomatic the following day. Two days later, he presented again to the ED because of a syncope preceded by a similar vagal reaction. The ICD worked properly, and no arrhythmias were found. Chest radiograph showed an area of lung

Figure 1  A: Unremarkable chest radiograph at the time of hospital admission. B: Chest radiograph showing right lower lobe pneumonia after hospitalization.

Figure 2  A: Computed tomography (CT) scan of the chest showing bilateral multiple ground-glass opacities. B: CT scan of the chest showing imaging improvement correlated with resolution of clinical symptoms.
dysventilation in the right lower lobe (Figure 3B). CT scan of the chest confirmed bilateral pneumonia, with multiple ground-glass opacities with subpleural distribution (Figure 3C). He was tested again for COVID-19 infection and the result was positive.

Discussion

We reported a case series of patients presenting with syncope as the only initial symptom of COVID-19 infection. To our knowledge, this finding has not been systematically described in the literature.

Syncope may be a very common chief complaint of patients presenting to the ED, with a broad differential diagnosis.2 Patients with syncope, especially when deemed vasovagal or orthostatic, are usually dismissed from the ED after a thorough clinical history evaluation. Our case series showed how syncope may be the presenting symptom of a very serious illness.

The mechanism behind the occurrence of syncope in COVID-19 has not been described. In our case series, cardiac syncope with tachyarrhythmia or bradyarrhythmia as the primary cause has been excluded, since all patients had a PPM or an ICD showing no abnormalities. Syncope due to structural cardiac disease or pulmonary embolism has been ruled out as well. The proposed pathophysiological explanation might be a neurally mediated/reflex mechanism in its nonclassical form (absence of certain trigger) or an autonomic dysfunction, either primary or secondary. There are 2 main pathophysiological mechanisms in reflex syncope, both of them depending on an imbalance between sympathetic and parasympathetic activity: vasodepression, caused by insufficient sympathetic vasoconstriction; and cardioinhibition, caused by parasympathetic predominance. This type of imbalance might find another confirming factor in the association between COVID-19 infection and “inappropriate” sinus tachycardia, which often characterizes patients with novel coronavirus infection even in the absence of respiratory failure.3

The autonomic failure hypothesis, on the other hand, might involve a primary failure caused by the virus itself or a secondary failure due to autoimmune autonomic neuropathy. The occurrence of neurologic features in COVID-19 infection has been recently documented, in terms of encephalopathy and corticospinal tract involvement.4,5 However, determining if this is a direct effect of the virus or if it is due to a critical autoimmune reaction or inflammation caused by cytokines is still a matter of debate. Cytokine storm with subsequent hyper-inflammation is one of the proposed mechanisms of COVID-19 serious illness.6 Vascular injury caused by IL-1 and IL-6 and decreased systemic vascular resistance resulting in vasodilation could be one of the possible explanations of syncope as the resulting symptom.7

Finally, 4 out of 5 patients in our series were on chronic therapy with angiotensin-converting enzyme (ACE) inhibitors. Whether ACE inhibitors, upregulating ACE-2 expression in many tissues and therefore facilitating virus binding to the cells, predispose to COVID-19 infection has not been proved.8,9 However, the overall decrease in the vasopressor effect of angiotensin II in patients treated with ACE inhibitors might play a role in the pathophysiology of syncope.

Further studies with larger sample size are necessary before drawing definite conclusions on the mechanism of syncope as the presenting symptom of COVID-19 infection. However, recognizing this possibility is of extreme importance, especially in the initial phase of COVID-19 infection, when the transmission rate might be very high and maximum isolation precautions are not in place yet.

Conclusion

We reported a case series of patients presenting with syncope as the only initial symptom of COVID-19 infection. Whether the exact mechanism is still debated, recognizing this
possibility is of utmost importance for undertaking appropriate isolation precautions and possibly for treating patients when the infection is still at its initial phase.

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