and right paratracheal nodes. Subsequent testing with RT-PCR was positive for SARS-CoV-2.

DISCUSSION

This case highlights the findings on 18F-FDG PET/CT in a nursing home physician suspected of COVID-19, raises a number of clinical dilemmas, and points to the potential use of PET/CT in studying the pathophysiology of COVID-19 as follows:

1. Our patient had two negative RT-PCR tests for SARS-CoV-2, confirming the high false-negative rate when compared with CT imaging. A review of seven previously published studies of both inpatients and outpatients with SARS-CoV-2 infection reported a wide variation in sensitivity of RT-PCR, depending on the time the test was taken after symptom onset. Specifically, the false-negative rate of RT-PCR tests was 38% on the day of symptom onset, 20% 3 to 4 days after symptom onset, and 66% 2 weeks after symptom onset. Other factors that could contribute to the two negative RT-PCR tests include sampling, storage, and processing errors and different viral loads, depending on stage of the disease. Most important, the sensitivity of chest CT for diagnosing COVID-19 has been shown to be 98% compared with 71% for RT-PCR.[5]
2. The 18F-FDG PET/CT findings in this patient are consistent with past studies showing multiple, bilateral FDG-positive GGOs, multilobar consolidations, and evidence of lymph node involvement.[6]
3. GGOs are often unperceivable on chest radiography, particularly in patients with few symptoms or low severity. Although we are not suggesting that routine 18F-FDG PET/CT scans be done on patients suspected of COVID-19, we believe the standard of care should be that patients with a clinical syndrome including respiratory symptoms and/or signs consistent with COVID-19, a negative chest X-ray, and neoplastic comorbidities have a chest CT scan.[7] Bilateral GGOs or consolidation on chest CT scan in the proper clinical situation should prompt the radiologist to suggest COVID-19 as a possible diagnosis.[8]
4. Findings consistent with COVID-19 will be found in patients having 18F-FDG PET/CT for either staging or recurrence of malignancies. Consequently, nuclear medicine departments and staff need to assume that all patients undergoing 18F-FDG PET/CT need to be screened before scanning, personnel properly gowned and masked, the facility properly cleaned and disinfected afterwards, and lung nodule evaluation be modified.[9]
5. FDG PET/CT is highly sensitive for detecting inflammatory disease and is a potential modality to study the inflammatory components of SARS-CoV-2 infections, monitoring disease progression and treatment effects and potentially improving patient management. In addition, FDG PET/CT may elucidate cytokine storm, focusing not only on pulmonary inflammation but also other organs that have been reported to be involved (i.e., myocardium, pericardium, and intestine).[10]

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COMMENTS

Long-Term Care Facilities and the COVID-19 Pandemic: Lessons Learned in Madrid

To the Editor: We have read with interest the excellent article by D'Adamo et al on the ABCDs of managing the coronavirus disease 2019 (COVID-19) pandemic in long-

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term care,[1] and we want to report our experience in Madrid, the hardest hit city by the pandemic in Spain.[1]

The Autonomous Community of Madrid is a Spanish region with a population of 6,662,000 people. It has one of the highest longevity rates in Europe, with 17.5% and 5.5% of its total population aged 65 years and older and 85 years and older, respectively. This region was first hit by the COVID-19 pandemic at the beginning of March 2020, with a rapid dissemination and an exponential increase in the number of contagions and deaths, particularly in older adults living in long-term care facilities (LTCFs). At the time the pandemic started, Madrid had approximately 480 LTCFs, housing approximately 44,000 older adults. Older patients living in LTCFs in Madrid were clearly the most vulnerable population during the pandemic. From March 8 to April 19, 2020, 19% of older patients (n ~ 8,300 cases) living in these facilities died, with a six-fold increase compared with the same period in the last years.

To provide guidance for coping with the spread of COVID-19 across LTCFs, here we will briefly discuss some important issues we have learned and should be kept in mind when providing care to patients living in these facilities (Figure 1).

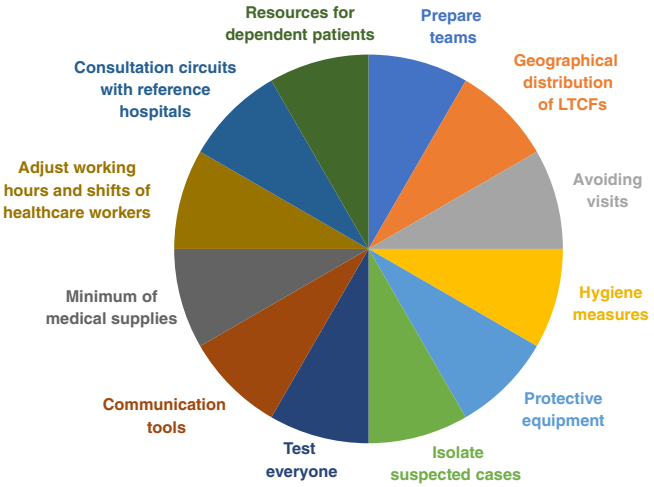


Figure 1. The 12 tips learned in Madrid, Spain, not to be missed for long-term care facilities (LTCFs) amid the coronavirus disease 2019 pandemic.

1. Make sure to have a team prepared to take care of this vulnerable population. In all countries affected by the pandemic, initial efforts focused on treating patients in acute-care hospitals and intensive care units.[2] Yet, once the pressure on acute care decreases, the sad reality of LTCFs is likely to emerge.
2. Be aware of the geographical distribution of LTCFs. Hospital catchment area volumes are often based on the general population, and do not take into account the number of patients living in LTCFs in the area, which can overload some hospitals.
3. Minimize contacts within the LTCFs, avoiding visits of family and friends.
4. Implement all the recommended hygiene measures for everyone working in—or visiting—the facilities: handwashing, use of face masks, surface disinfection, and cloth washing.[3]
5. Provide appropriate protective equipment to avoid high risk of contagion among staff members. In the case of LTCFs, it is also essential to protect caregivers who may visit the facilities.
6. Isolate suspect cases. In a pandemic situation, any individual with respiratory symptoms should be considered suspicious, and isolation should be performed.
7. Test everyone you can, the more the better. To implement successful isolation measures, it is essential to first identify those individuals who are infected, including the asymptomatic ones who are potent transmitters.
8. Because the patient will be much more isolated than normal, implementing communication tools, such as videoconferences, will anticipate this problem and will not add more despair to relatives.
9. Provide facilities with a minimum of supplies (oxygen, intravenous solutions and lines, antibiotics, morphine, and sedatives).[4] We have observed that in some areas of Madrid, requests for oxygen have increased by 400%. It is essential to define a series of minimum resources that each center must have, depending on the total number of residents and of affected people among them, and to establish effective circuits to replenish them.
10. If possible, adjust working hours and shifts to decrease the risk of infection among healthcare workers. We propose the creation of shifts of a shorter duration throughout the week.
11. Establish consultation circuits with hospitals to discuss cases and decide on the most appropriate treatment. In the case of Madrid, a geriatrician was the "coordinator physician," who is available to guide workers at the facilities.
12. Make resources available for patients with dependency. Those transferred to a COVID-19 area could lose their routine resources and make it more difficult to assist them properly.

In conclusion, the high fatality rate among older adults living in LTCFs in Madrid during the COVID-19 pandemic showed us our strengths, such as being aware of the geographical distribution of all LTCFs and keeping in close contact between hospitals and LTCFs in a consolidated continuing healthcare program led by a hospital-based geriatrician. What we failed to do was not to reallocate resources earlier, as we focused first in acute care in tertiary hospitals, and not to test as many patients as possible to implement better successful isolation measures. We learned the importance of minimizing contacts, applying stringent hygiene measures, and providing protective equipment to staff members.

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Neurological, Cognitive, and Behavioral Disorders during COVID-19: The Nitric Oxide Track

To the Editor: Coronavirus disease 2019 (COVID-19) exhibits a wide range of clinical signs, especially in older adults.[1] Alkeridy et al recently reported an interesting case of delirium with lower limb sensorimotor disorders in a 73-year-old man with otherwise asymptomatic COVID-19.[1] The mechanism proposed by the authors was based on the invasion of the nervous system by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, as previously described in a COVID-19 case with encephalitis.[2] Although acknowledging the value of this assumption, we discuss here the likely role of a third player, namely nitric oxide (NO), to explain the onset of neurocognitive disorders in patients with COVID-19.

NO, originally known as an endothelium-derived relaxing factor, is a gaseous membrane-soluble neurotransmitter synthesized endogenously from L-arginine, oxygen, and nicotinamide adenine dinucleotide phosphate by various nitric oxide synthase enzymes.[3-5] Studies in experimental animals have well documented the synthesis of NO in the brain and its role in a variety of neuronal functions including learning and memory processes or locomotor activity.[3]

Although it plays an important role in cell signaling in the brain, NO was described as an "unconventional" neurotransmitter. Indeed, it is neither stored in synaptic vesicles nor released upon membrane depolarization; it is directly released upon synthesis.[4] Also, NO does not mediate its action by binding to some membrane-associated receptors, but it diffuses from neuron to neuron to act on intracellular components.[4] NO functions as a neurotransmitter by stimulating soluble guanylyl cyclase to form a second messenger molecule, cyclic guanosine monophosphate (cGMP), in target cells. The cyclic nucleotide cGMP relaxes vascular smooth muscles with consequent vasodilation and increased blood flow. Increased intracellular cGMP level was shown to contribute to excessive neuron excitability and locomotor activity.[6] The decrease in NO concentrations in the brain was consistently found to induce cognitive and behavioral disorders in various experimental animals.[5]

On this basis, we propose that some of the neurological signs in patients with COVID-19 are associated with the virus-induced decrease in NO levels in the brain. The production of NO is tightly linked to the renin-angiotensin system (RAS), precisely targeted by SARS-CoV-2[7] that was described to overactivate the RAS by interacting, via its spike (S) glycoprotein, with the metallopeptidase angiotensin-converting enzyme 2 (ACE2) receptor,[7] expressed at the surface of numerous cell types including cerebral neurons.[8]

In RAS, angiotensin II, by acting on the vasoconstrictor type 1 angiotensin II receptor (AT_1R), reportedly diminishes the production of NO,[9] leading to an expected decrease in NO concentrations in the brain during COVID-19, which needs to be compensated to prevent neurological cognitive and behavioral disorders. Because NO is basically too reactive (with a very short half-life of 5 seconds) to constitute an appropriate therapeutic target, a strategy would be to counterbalance RAS overactivation and thus maintain the appropriate NO levels in the nervous system. Interestingly, previous work to increase NO concentrations in the brain with specific agents known to elevate NO production was found to improve memory in experimental animals.[5]

In human COVID-19, proposed chemotherapeutic drugs to limit/counterbalance the overactivation of RAS could be ACE inhibitors (to prevent the production of angiotensin II from angiotensin I), blockers/antagonists of AT_1R such as losartan and derivatives, and also some natural candidate peptide drugs that belong to the so-called counterregulatory RAS (i.e., angiotensin 1–7, angiotensin 1–9, alamandine, angiotensin A, and/or angiotensin IV).[10] All these molecules are expected to counteract the SARS-CoV-2-induced overactivation of RAS, to maintain NO production, and to reverse, to some extent, the associated neurological cognitive and behavioral disorders in COVID-19.

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See the Reply by Alkeridy et al.

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