An Agitated Patient With COVID-19 Infection and Early-onset Alzheimer Disease

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Abstract: Encephalopathy, delirium, and agitation are documented symptoms of coronavirus disease (COVID-19) infection, but research into the management of agitation in the setting of COVID-19 and pre-existing neuropsychiatric disease is ongoing. We present a 55-year-old male patient with early-onset Alzheimer disease and deteriorating mental and functional status who presented to our institution with agitation and persistent COVID-19 positivity on polymerase chain reaction testing. His agitation was improved through pharmacologic optimization including the avoidance of benzodiazepines and initiation of clonidine and prazosin, which temporally coincided with the resolution of his nearly 2-month long COVID-19 positivity.

Key Words: early-onset Alzheimer disease, agitation, aggression, sedation, COVID-19, encephalopathy

(*Alzheimer Dis Assoc Disord* 2022;36:83–84)

Preliminary studies have described the neurological manifestations of coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), as encephalopathy or altered sensorium.[1] An even more uncharted territory is the intersection between COVID-19 and pre-existing neuropsychiatric comorbidities. Patients with dementia are not only at high risk for morbidity and mortality, but are also more susceptible to mental health sequelae of COVID-19.[2,3] We present a patient with early-onset Alzheimer disease (AD) who presented to our institution with agitation and COVID-19 infection.

CASE DESCRIPTION

Mr R. is a 55-year-old male with early-onset AD diagnosed in 2014 on the basis of history, exam, brain magnetic resonance imaging, fluorodeoxyglucose-positron emission tomography pattern typical of AD, and cerebral spinal fluid amyloid and tau protein markers after ruling out several metabolic, autoimmune, infectious, and other etiologies. Genetic testing did not demonstrate any known mutations in genes associated with early-onset AD and his disease was thus suspected to be sporadic. Because of progressive cognitive and functional decline, as of August 2019 his Short Test of Mental Status score was 15/38 and he was living in a group home.

In September 2020, he was hospitalized in a geropsychiatric unit for new onset aggression, where he was found to be positive for SARS CoV-2, though asymptomatic from a respiratory perspective. However, after his COVID-19 infection, his mentation continued to worsen and he was minimally responsive with disorganized, flailing movements. He had paradoxical reactions to quetiapine, olanzapine, and ketamine, manifesting as aggression and akathisia. He was discharged to a new group home on dextromethorphan-quinidine, galantamine, lorazepam, and trazodone.

In November 2020, 1 week after his discharge, he once again became aggressive and presented to our emergency department. He was afebrile and hemodynamically stable but attempted to strike staff members. His SARS CoV-2 polymerase chain reaction (PCR) test at our institution was positive. Other laboratory studies showed only mild stable normocytic anemia. Computed tomography imaging of his brain without intravenous contrast demonstrated moderate diffuse parenchymal atrophy with enlarged ventricles and sulci, which were slightly increased from 1 year prior, but with no acute intracranial abnormality (Fig. 1). His home medications were continued with lorazepam ordered as needed for agitation.

The patient's hospital course lasted 23 days. He experienced significant combative behavior soon after admission and required soft restraints and frequent lorazepam administration which was minimally effective. After consultation with neurology and psychiatry, he was started on clonidine 0.1 mg twice daily for agitation. Trazodone was initially continued but mirtazapine and trazodone were alternated several times during his admission with no major symptom relief. He responded favorably to clonidine 0.1 mg bid and experienced about 1 h of sedation and anxiolysis. Clonidine was therefore increased to 0.2 mg bid which he could not tolerate because of hypotension.

Pharmacologic interventions had thus far proved insufficient to control his agitation and he had another episode of aggression to nursing staff, resulting in denial of his transfer to memory care. Citalopram was initiated for long-term agitation control. We prescribed prazosin 1 mg nightly with plans to increase this dose every 2 to 3 days until reaching a target dose of 6 mg nightly. Unfortunately, because of hypotension, prazosin dose could not be increased further. Lorazepam was discontinued.

With discontinuation of lorazepam and initiation of prazosin, his agitation improved and soft restraints were removed. The patient underwent evaluation by local memory care units. During his stay, he had 3 SARS CoV-2 PCR tests which were positive and a fourth final negative PCR (over 2 months after his original infection), eliminating the last barrier to discharge. At the conclusion of his hospital course, his psychiatric regimen included citalopram, clonidine, galantamine, melatonin, dextromethorphan-quinidine, and prazosin. Upon discharge to a memory care unit, he was sleeping 6 hours per night, ambulatory, but requiring full assistance with activities of daily living.

DISCUSSION

As the manifestations of COVID-19 infection include widely distributed physiological effects, so does the care of patients with severe infection require familiarity with rapidly evolving research. Management of agitation is an indispensable part of caring for patients with COVID-19. Here we present our management of a patient with early-onset AD who subsequently experienced COVID-19 infection with persistent PCR positivity, a lack of hallmark disease symptoms, and worsening agitation.

Citalopram was initiated off-label during hospitalization based on its demonstrated calming effect in patients with AD, but a more rapid anxiolytic and sedating strategy was needed.[4] His previous adverse reactions to antipsychotics and ketamine complicated our management. While antipsychotics

Received for publication December 13, 2020; accepted April 1, 2021.
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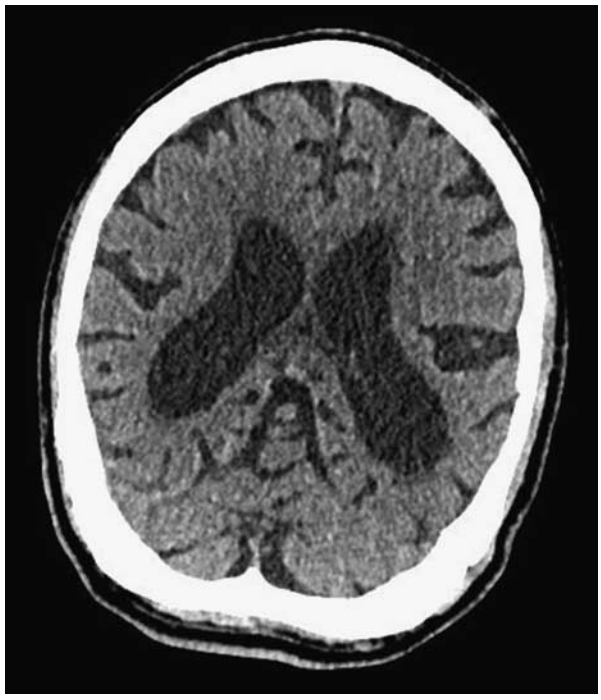

FIGURE 1. Computed tomography of the brain without intravenous contrast obtained on admission demonstrated moderate diffuse parenchymal atrophy with enlarged ventricles and sulci, which were slightly increased from 1 year prior, but with no acute intracranial abnormality.

would have been useful during periods of aggression, his prior paradoxical reaction or akathisia was such that we pursued alternative pharmacological strategies.

Benzodiazepines are a key class of medications for control of anxiety and aggression. Since the patient did not have a reported adverse reaction to benzodiazepines on admission, lorazepam was initially prescribed.[5] Use of benzodiazepines has thus far appeared efficacious in management of acute anxiety in patients with COVID-19, though prudence is required to avoid adverse respiratory depression. Our patient's respiratory status was fortunately preserved, so benzodiazepines appeared to be a worthwhile option. With Mr R's severity of dementia and risk of worsening delirium, the inefficacy of lorazepam is not highly surprising, though we do maintain that a trial was clinically reasonable because of his poor tolerance of antipsychotic medications.

Given his recent COVID-19 infection reportedly exacerbated his symptoms per outside records, we considered the use of clonidine based on the pharmacologic recommendations proposed by Baller et al.[6] Clonidine is sometimes used off-label in intensive care units as an alternative sedative agent, particularly when transitioning from dexmedetomidine. It has successfully been adopted for this purpose in mechanically ventilated patients with COVID-19.[7] Our patient responded favorably to clonidine experiencing ~1 h of anxiolysis, but experienced hypotension at higher doses. Since clonidine could not be further increased, prazosin was also considered as a possible adjunctive therapy. Given the role of catecholamines in facilitation of the cytokine storm, prazosin is currently being studied as a potential treatment for symptomatic hospitalized COVID-19 patients.[8,9] Prazosin has also been demonstrated to be effective in treatment of agitation and depression, especially when underlying dementia is present, though its use for this indication is still under investigation.[10]

Addition of nightly prazosin was greatly anxiolytic for our patient. His sleep was more restful and restraints were removed entirely. While the favorable psychiatric response was promising, we would have preferred to ideally establish the patient on either clonidine or prazosin monotherapy to avoid simultaneous alpha-1 antagonism and alpha-2 agonism. However, given the refractory nature of his agitation, we ultimately decided to continue dual therapy as opposed to further medication adjustments to minimize the risk of recurrent agitation.

Though the patient's long-term neuropsychiatric prognosis remains poor, his hospital course concluded with significant improvement in the agitation which was a barrier to memory care. With no cerebral spinal fluid analysis, our ability to further clarify the extent of central nervous system involvement of COVID-19 is limited. Despite this fact, the resolution on PCR of the patient's COVID-19 infection also temporally coincided with the improvement of his symptoms, so we attribute his improvement to the combined resolution of his COVID-19 infection and appropriate adjunctive psychiatric medications.

CONCLUSION

As global understanding of the pathophysiology of the neuropsychiatric symptoms of COVID-19 infection evolves, formulation of standardized and validated guidelines will be essential to address new symptoms which arise in patients with underlying dementia and to manage existing symptoms in the setting of acute illness. Further research is required to determine the best approach for treating agitation or delirium in patients with COVID-19 and comorbid neuropsychiatric disease.

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