Acute Confusion as an Initial Presentation of SARS-CoV-2 Infection

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\textbf{Background and Purpose} The respiratory manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been extensively documented. There is emerging evidence that coronavirus disease 2019 (COVID-19) has number of other presenting features which might not be related to the severity of the respiratory disease. We have previously described a case of hypoactive delirium as the first manifestation of COVID-19 without profound lung disease. Here we present five cases of elderly patients, without a prior history of dementia and had no overt COVID-19-related pneumonia, who presented with the acute onset of delirium as the primary manifestation of COVID-19.

\textbf{Methods} This retrospective, single-center study performed a health informatics search to produce a list of patients who were admitted with acute confusion and tested positive for the SARS-CoV-2 virus between March 1 and June 30, 2020. The electronic medical admission notes were screened for all patients with confusion who tested positive for SARS-CoV-2. Patients with a history of dementia and a high risk of delirium were excluded, such as severe COVID-19-related pneumonia or any other infection, malignancy, drugs, or severe illness of any kind.

\textbf{Results} During the first wave of the COVID-19 pandemic our hospital experienced just over 3,000 SARS-CoV-2 positive patients, and 45 of them had documented confusion upon admission. Secondary causes for their acute confusion were excluded. Five patients were identified as having delirium as the initial presentation of COVID-19-related illness without significant COVID-19-related pneumonia. None of them had overt chest symptoms or a previous history of confusion, and the 3 patients who underwent head CT scans had normal findings.

\textbf{Conclusions} This case series illustrates the importance of recognizing acute confusion as the first manifestation of COVID-19 in susceptible individuals.

\textbf{Key Words} delirium, SARS-CoV-2, COVID-19, neuropathology.

\section*{INTRODUCTION}

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).\textsuperscript{1} This is now a global pandemic that is showing no sign of slowing down. Most patients infected by SARS-CoV-2 develop mild to moderate symptoms such as fever, dry cough, and fatigue, which resolve without the need for hospitalization.\textsuperscript{2,3} The vast majority of patients requiring hospital admission present with moderate or severe COVID-19-related pneumonia with symptoms restricted to the respiratory system. However, similar to any severe disease that causes respiratory distress, COVID-19 can manifest in a multisystem manner that leads to acute insult to the cardiovascular, renal, hematological, and metabolic systems, as well as the peripheral nervous system.

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(PNS) and the central nervous system (CNS). The neurological manifestations involving the CNS and PNS vary, and most commonly are myalgia, headache, confusion, and loss of taste and smell. In addition, case reports/series have documented uncommon neurological manifestations such as Bell's palsy, Guillain-Barré syndrome, acute myelitis, encephalitis, and ischemic and hemorrhagic stroke.

We have previously reported a single case in which prolonged confusional state was the first manifestation of COVID-19. Based on screening 3,566 patients admitted to our hospitals with COVID-19, here we report a case series of 5 patients who developed acute confusional symptoms as the primary manifestation of COVID-19 without overt respiratory symptoms.

METHODS

This retrospective, observational study was conducted at the University Hospital of Birmingham, UK. We undertook a health informatics search to produce a list of patients who were admitted with acute confusion and tested positive for the COVID-19 virus between March 1 and June 30, 2020. During that period, our hospital experienced just over 3,000 admitted SARS-CoV-2-positive patients, and 45 of them had documented confusion. Their electronic medical admission notes were screened, and patients with a history of dementia and a high risk of delirium were excluded, such as severe COVID-19-related pneumonia or any other infection, malignancy, drugs, or severe illness of any kind. Patients whose presenting symptoms included acute confusion and who tested positive for the COVID-19 virus without severe respiratory symptoms were enrolled in this study. Their detailed clinical information was obtained from their medical records, families, and caregivers to determine whether their clinical symptoms of confusion were likely to be related to COVID-19 and predated severe COVID-19-related pneumonia. Great care was taken to exclude other causes of confusion.

Data gathered as part of the clinical care and audit of the clinic were approved by the trust audit office (CARMS-16371).

RESULTS

Table 1 lists the characteristics and clinical courses of the patients. Their age at the time of presentation was 78.2 ± 3.3 years (mean ± SD). Four of them were male, and all patients initially presented with an altered mental status that included confusion, agitation, refusing care, and falling. All five patients were positive for the COVID-19 virus in swab tests using RT-PCR, but none of them had the classical presentation of severe respiratory symptoms. All five patients also had no previous history of confusion, were able to perform self-care, and lived independently either with a partner or alone. All patients had an oxygen saturation at admission of > 95% when breathing air. CT scans of the head were normal, with no evidence of chronic disease or acute intra- or extra-axial hemorrhage. Chest X-rays in all five patients showed bilateral patchy air-space opacification suggestive of COVID-19-related pneumonia. Three of the five patients died in hospital, and the other two were discharged home. The patient presentations are described in detail below.

Case descriptions

Case 1

A 77-year-old male was admitted to the emergency department with fluctuating confusion and recurrent falls of 3 days duration. He had recently been experiencing a cough that was suspected to be COVID-19. He was previously well, lived with his partner independently, walked about 1.5 km each day, and could drive. On admission he was inattentive, with a Glasgow Coma Scale (GCS) score of 14/15, afebrile, and had an oxygen saturation of 95% when breathing air.

This patient was admitted with suspected mild COVID-19-related pneumonia and hypoactive delirium. Biochemical and hematological investigations were satisfactory apart from elevated C-reactive protein (CRP) at 66 mg/L. He was commenced on amoxicillin and intravenous (IV) fluids. At 1 day postadmission he developed temperature spikes, and over the subsequent days became hypoxic so as to require high-flow oxygen via a facemask, and the IV antibiotics treatment was escalated to Tazocin. However, his condition gradually deteriorated, and he died 14 days later.

Case 2

An 80-year-old female was admitted to hospital after an episode of confusion that had started 2 weeks previously. Prior to this incident she was healthy, living alone, and could independently perform all of the usual activities of daily living. Her general practitioner (GP) thought her delirium was secondary to a urinary tract infection (UTI) or community-acquired pneumonia and so she was given antibiotics, to no avail. On admission she was orientated to place but not time or person, and she was uncooperative. All of her vital signs were within the normal limits, and other neurological examinations were unremarkable. Biochemical and hematological parameters were all within the normal limits, except for slight leucocytosis, increased CRP at 48 mg/L and urea at 10.3 mmol/L, and low albumin at 25 g/L.

The patient was treated with IV fluids and IV antibiotics and made a full recovery and was discharged home at 8 days.
| Table 1. Summary of the patients demographics and clinical details |
|---------------------------------------------------------------|
| **Patient** | **1** | **2** | **3** | **4** | **5** |
| Age (years)/sex  | 77/male | 80/female | 77/male | 80/male | 77/male |
| Presenting symptoms  | Fluctuating confusion and falling | Fluctuating confusion | Confusion and falling | Hypoactive delirium | Confusion |
| Swab positive for SARS-CoV-2  | Yes | Yes | Yes | Yes | Yes |
| Chest X-ray on admission | Patchy ground-glass opacity in both middle and lower zones with a peripheral distribution | Extensive areas of air-space opacification particularly in the left middle and lower zones, and also within the right lower zone | Air-space opacification in the right lower zone and left peripheral middle and upper zones | Shadows in the right-side peripheral, middle, and lower zones | Bilateral pulmonary infiltrates in the middle and lower zones |
| Head CT | No acute intracranial pathology | No acute lesion seen. Findings within normal limits | Normal findings with no evidence of intra- or extra-axial hemorrhage | Not done | Not done |
| Comorbidities | Hypertension, type II diabetes, previous prostate cancer, atrial fibrillation | Hypertension, previous breast cancer | Hypertension | Hypertension, bipolar disorder | Hypertension, diabetes mellitus, hypercholesterolemia, asthma, hypothyroidism |
| Medications on admission | Ramipril, atorvastatin, metformin, linagliptin | Ramipril, atorvastatin | Enalapril, indapamide, atorvastatin, aspirin, lansoprazole | Doxazosin, simvastatin, gabapentin, nebivolol, lithium | Ramipril, bisoprolol, felodipine, metformin, simvastatin |
| Outcome | Died after 14 days from severe COVID-19-related pneumonia | Fully recovered and discharged home after 8 days | Died after 4 weeks of a hospital-acquired infection | Died after 8 days | Fully recovered and discharged home after 36 days |
| Sodium on admission (mmol/L) | 137 | 142 | 139 | 156 | 143 |
| Potassium on admission (mmol/L) | 4.6 | 4.6 | 3.8 | 3.8 | 3.5 |
| Calcium on admission (mmol/L) | N/A | 2.16 | 2.14 | 2.72 | 2.15 |
| Urea on admission (mmol/L) | 6.6 | 10.3 | 8.2 | 10.2 | 13.3 |
| Creatine on admission (μmol/L) | 95 | 63 | 94 | 172 | 151 |
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postadmission.

Case 3
A 77-year-old male who was normally fit and well was admitted with acute confusion and falling when climbing stairs. On examination, the patient was awake but inattentive, with a GCS score of 14/15. Biochemical investigations revealed low sodium (139 mmol/L) and elevated CRP (44 mg/L). Treatment with levofloxacin at 500 mg daily for 5 days and IV 0.9% normal saline resulted in his sodium levels normalizing over a few days, but the patient remained confused. He died at 4 weeks postadmission due to a hospital-acquired infection. Details of this case have been reported elsewhere.7

Case 4
An 80-year-old male was admitted to hospital with the sudden onset of agitation and confusion of 4 days duration. The patient had a cough of 1 week duration prior to his admission. He was otherwise well, independently mobile, and able to perform self-care. On examination, he was disoriented with motor perseverations. He was afebrile with a BP of 143/88 mm Hg, pulse of 106 beats/min, respiration rate of 20 breaths/min, and oxygen saturation of 97% when breathing air. He was dehydrated with high levels of sodium (156 mmol/L), urea, creatine, and hemoglobin. He was treated with IV fluids, IV antibiotics, and strict fluid balance, but remained confused. Three days later he developed temperature spikes and then became hypoxic, requiring oxygen supplementation. His condition gradually deteriorated, and he died at 8 days postadmission.

Case 5
A 77-year-old male who was normally fit and well was admitted with acute confusion and falling when climbing stairs. As the COVID-19 worldwide pandemic continues to unfold, the extent of the multisystem nature of the disease continues to evolve. An area of increasing interest is the effect of SARS-CoV-2 on the CNS. Mao et al.9 reported that 36.4% of 214 patients had neurological manifestations, including headache, nausea, vomiting, confusion, ataxia, acute cerebrovascular disease, and seizures. In addition, Chen et al.10 noted that 9% of 99 patients with severe COVID-19 on admission to hospital exhibited acute confusion, which they attributed to severe hypoxia or multiorgan failure. However, we and other authors have shown direct neurological complications of SARS-CoV-2, including neuropsychiatric symptoms as a first manifestation,7 encephalitis,7 transverse myelitis, and Guillain-Barré syndrome.4

In line with the primary CNS manifestations described above, our five patients were admitted with the acute onset of confusion and without significant respiratory symptoms or evidence of hypoxia. The findings were normal in all three patients who underwent head CT scans except from the common age-related changes, showing that these symptoms could not be attributed to intracranial pathology. Our high workload during the pandemic prevent us from performing any brain MRI scans, and so the possibility of acute brain lesions in these cases cannot be fully excluded. Some chest changes were seen in chest X-rays, but none of the patients required ventilation or high-flow oxygen at admission. Hypoxemia and hypoglycemia are two self-evident causes of acute brain dysfunction that can impair attention and cognition,11 but these conditions were excluded from the present cases. In addition, we ruled out common risk factors that predispose patients to delirium such as underlying dementia or cognitive impairment, multiple comorbid diseases, other infection, pre-existing severe illness, poor functional baseline, and malnutrition.12 However, old age and acute illness in our patients were risk factors that we were unable to exclude since all of them were older than 75 years.

All of the study subjects had a CURB 65 severity score of 2 for their pneumonia severity despite the chest X-ray findings classifying them as moderate severity. Dehydration and electrolyte imbalance were also ruled out as a cause of their acute confusion. Each patient was older than 75 years and did not have premorbid cognitive impairment and where independent in activities of daily living based on their caregiver descriptions and medical records. It is therefore possible that some of them had underlying mild cognitive impairment before admission that was unmasked by the acute COVID-19 illness.

DISCUSSION

This case series illustrates that acute confusion may be the dominant presenting feature of COVID-19 in elderly patients. It reinforces our understanding that delirium in the elderly is usually a manifestation of another disease, and that it can occur before more classical features in COVID-19. In all five cases, great care was taken to exclude other diseases that could have caused delirium.

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The mechanisms underlying altered consciousness in patients with COVID-19 without hypoxia or vascular event are unknown. Two similar human coronaviruses that cause severe acute respiratory syndrome (SARS) and the Middle Eastern respiratory syndrome (MERS) have been shown to have neurotropic and neuroinvasive properties, and cause disease in the CNS and PNS.13 Although it is unclear if SARS-CoV-2 is neurotropic in humans, neuroinvasion via several routes has recently been proposed, including transsynaptic transfer across infected neurons, entry via the olfactory nerve, infection of the vascular endothelium, or leukocyte migration across the blood–brain barrier.14 In addition to direct viral neuroinvasion into the CNS, it is plausible that delirium can be caused by changes mediated via crosstalk, such as proinflammatory cytokines and prostaglandins, with the action of inflammatory mediators being less restricted by the blood–brain barrier.15 Zeng et al.16 reported that inflammatory markers, and especially CRP, procalcitonin, interleukin 6, and erythrocyte sedimentation rate, are positively correlated with the severity of COVID-19. Macullich et al.17 showed that alterations of behavior during immune stimulation may be coordinated by the synthesis of proinflammatory mediators in the CNS, where a systemic inflammatory signal can be transduced into the brain without any compromise of the blood–brain barrier.18 Circulating inflammatory mediators can interact directly with neurons in an aging brain where there is partial compromise of the blood–brain barrier in susceptible individuals.

In summary, delirium may be the only early symptom of COVID-19 infection in elderly individuals that appears before respiratory symptoms develop. Early recognition of the range of clinical manifestations associated with COVID-19 may lead to improved clinical outcomes.

**Author Contributions**

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**Conflicts of Interest**

The authors have no potential conflicts of interest to disclose.

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