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Significant cognitive impairment likely associated with COVID-19 infection with relatively nonsevere symptoms

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Abstract: COVID-19 infection may involve the nervous system and has been associated with a number of neuropsychiatric complications, including impairment of cognition and dementia. Such complications are more likely to occur in (but are not limited to) patients with severe COVID-19 infections and those with concomitant risk factors. In this case report, the authors describe a normally functioning 51-year-old woman who developed cognitive impairment of a degree that rendered her unable to care for herself most likely related to a relatively nonsevere infection with COVID-19 about 2 months earlier. A detailed report of her deficits of different areas of cognitive functioning is provided. This report aims to make clinicians more aware of the potential for cognitive impairment in patients who have suffered from COVID-19, including those with infections that were not severe.

Keywords: cognitive decline; coronavirus-19; COVID-19; Montreal Cognitive Assessment.

COVID-19 is primarily a respiratory disease, but there is increasing evidence that coronaviruses can spread to extrapulmonary organs, including the central nervous system (CNS) [1–3]. Neurological and neuropsychiatric complications, including cognitive impairment, are being increasingly reported [4, 5]. Cognitive impairment may vary in intensity and in time of onset relative to COVID-19

infection, but long-term studies of this and other COVID-19 complications are not yet available [6].

Human coronaviruses may cause cognitive impairment by damage to the CNS through direct neurotoxicity or activation of the host immune response [2]. It is unclear how much of the damage is mediated by direct or inflammatory effects of the virus on the CNS and how much is secondary to extracranial cardiorespiratory disease [7]. There are at least four pathogenic mechanisms that may account for the detrimental effects of COVID-19 on the CNS: (1) direct viral encephalitis, (2) systemic inflammation, (3) peripheral organ dysfunction, and (4) cerebrovascular changes [8]. Whether a specific patient would be at risk for developing cognitive impairment may be difficult to determine. There is clearly a need among practitioners for increased awareness of potential cognitive impairment in patients who suffered from COVID-19, including those who had relatively mild infections, to help reduce diagnostic delay. We hope this case report of a woman who developed significant cognitive impairment most likely related to a COVID infection with mild symptoms will contribute to that increased awareness.

Case description

The patient described in this report is a 51-year-old woman admitted to a state psychiatric facility on April 12, 2021 because of inability to care for herself. She had been in good health and according to multiple family and friends was living independently, employed as a factory worker, and doing well until December 2020. However, between then and February 2021, she experienced marked deterioration of her cognitive abilities. Her medical history included joint pain, back pain, and gastroesophageal reflux disorder. There was no history of mental illness. There was no history of misuse of drugs or alcohol, and she had never smoked.

On December 9, 2020, the patient developed a fever and tested positive for COVID-19. Afterwards she developed nausea, vomiting, cough, and malaise. On December 17,

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2020, she presented to a primary care physician (PCP) complaining of decreased appetite and diarrhea. Her temperature was 100.6°, her SpO₂ was 100% on room air, and her white blood cell (WBC) count was 7,200. She was instructed to complete a 4-day course of azithromycin to prevent bacterial infection.

On December 28, 2020, she presented with complaints of cough, mild exertional dyspnea, and nausea. Her temperature was 99.5°, her SpO₂ was 98% on room air, and her WBC count was 13,200. Her chest X-ray was unremarkable, and her lungs were clear to auscultation bilaterally. The evaluating clinician described her as “minimally symptomatic ... nontoxic appearing.” She was treated with cefdinir 300 mg b.i.d. for suspected bacterial infection, aspirin 81 mg daily to help prevent inflammation and coagulopathy, and ondansetron as needed for nausea. Her symptoms then resolved.

On January 15, 2021, she was seen for abdominal discomfort thought to be secondary to taking ibuprofen for joint pain. Her temperature was 98.1°, her SpO₂ was 100% on room air, and her lungs were clear to auscultation. An examination revealed no signs of active COVID-19. Subsequently, she had no contact with any medical professional until mid-February.

In early February (exact timing unclear), she began experiencing cognitive difficulties. On February 18, 2021, she was hospitalized at a regional medical center and described as having “a subacute/progressive severe deterioration of neurological function including cognition, speech, language, and motor skills.” Neurological examination revealed that cranial nerves II–XII were intact without deficit. Her motor function was intact with muscle strength 5/5 bilaterally. Sensation of pain, position, and vibration were intact bilaterally. Her deep tendon reflexes were 2/4 and symmetrical bilaterally. Her cerebellar function was intact, and no abnormalities of coordination or gait were noted. Workup did not reveal a specific cause, although she was believed to have complications related to COVID-19. She was discharged on March 11, 2021 but was admitted to a small county hospital the next day, where she continued to exhibit signs of cognitive impairment. She complained of abdominal discomfort and stopped eating. A PEG tube was placed. She was believed to be psychotic and was started on aripiprazole 15 mg daily and diazepam 5 mg twice daily. She was then referred to the psychiatric hospital on April 12, 2021.

At the psychiatric hospital, physical examination was unremarkable except for right upper quadrant abdominal tenderness and pain of the lower extremities with passive range of motion. Paravertebral muscle spasm was present bilaterally from T6 to T10, and worse on the right. She

appeared moderately sedated. She demonstrated significant cognitive impairment, but during her entire stay at the psychiatric hospital, she had no hallucinations, delusions, or disorganization of thought processes, and it was felt that the conclusion by the physician at the county hospital that she was psychotic was incorrect. Aripiprazole and diazepam were discontinued because these medications may have been compromising her cognitive status. She became more alert and complained of abdominal pain. She underwent a cholecystectomy with complete resolution of her abdominal symptoms. She began eating, and the PEG tube was removed. She had feelings of sadness, decreased interest in activities, and loss of energy, and met the DSM-5 criteria for unspecified depressive disorder [9]. She was treated with sertraline 50 mg daily and behavioral activation with resolution of these symptoms. She was evaluated by a rheumatologist who noted pain in both knees and the left hip. The rheumatoid arthritis (RA) Latex test was positive. She was diagnosed with RA, and treatment was initiated with hydroxychloroquine 200 mg twice daily. He recommended not utilizing steroids at that point because of “the patient’s psychological issues.” Osteopathic manipulative treatment (OMT) included soft tissue massage and muscle energy techniques, and she received physical therapy.

Upon admission to the psychiatric hospital, she had demonstrated profound impairment of cognition, some of which was possibly due to sedating medications. With time, her cognitive status improved enough that she could communicate easily but not to the point that she could sufficiently care for herself. She continued to demonstrate significant difficulty with attention/concentration/working memory tasks, delayed recall, visuospatial skills, and executive functioning. On July 12, 2021, after reaching maximal improvement, her Montreal Cognitive Assessment (MoCA) score was 16/30 and her Hopkins Verbal Learning Test – Revised (HVLT-R) revealed significant memory impairment: Total Recall (T=25, <1st percentile) and Delayed Recall (T=32, 3.6th percentile). On that date (just prior to discharge), analysis of her cognitive functioning from these and other examinations revealed that she was able to correctly identify the date, month, year, day of the week, and city, but not the name of the hospital. She knew the president and the preceding president but not the president before him. She could not copy simple figures. She could not consistently repeat five digits forward or three digits backward. She could perform simple addition but not subtraction, but she was unable to perform serial addition or subtractions. She recalled 0/3 items at 3 min, and 0/3 with prompting. She was able to spell four- but not five-letter words in reverse. She evidenced difficulty with

some aspects of language and could not fully repeat sentences. She was unable to perform tasks that required higher executive functioning, such as planning to buy groceries or take a trip. Her judgment was poor, as evidenced by her making occasional disinhibited statements. On the Color Trails Test (CTT) administered to further evaluate executive functioning, her performance speed on the Color Trails 1 was in the average range for her age and education ($T=45$, 31st percentile). However, her performance on Color Trails 2, which requires greater sequencing skills and divided attention, was slow ($T=31$, 3rd percentile).

A summary of the diagnostic evaluations at the three hospitals includes unremarkable MRIs of the brain without contrast on February 22, 2021 and April 29, 2021. An EEG on February 24, 2021 showed mild diffuse background slowing (6–7 Hz), yet a repeat EEG on May 3, 2021 revealed normal background activity. Lumbar puncture revealed that her WBC count was 1 cell/ μL , red blood cell (RBC) count was 1,380 cells/ μL (suspected traumatic tap), glucose 75 mg/dL, protein 52, and negative cytology. Except in the early phases of her illness, complete blood counts (CBCs) were unremarkable. Comprehensive chemistry survey, liver function tests, chest X-ray, EKG, urinalysis, prothrombin time (PT) test, partial thromboplastin time (PTT), and international normalized ratio (INR) were unremarkable. Rapid plasma reagin (RPR), HIV, and hepatitis screening were negative. C3 was 138 mg/dL, C4 was 26 mg/dL, C-reactive protein was <1 mg/L, and uric acid was 5.2 mg/dL. Vitamins B1, B12, D, and folate levels were within normal limits. Erythrocyte sedimentation rate (ESR) ranged from 119 to 65 mm/h (normal 0–40 mm/h). The antinuclear antibody (ANA) test was negative, while the RA Latex test was positive. Of these results, the only abnormal ones were the ESR and the RA Latex tests.

As of July 2021, she had shown no additional improvement in her cognitive function and was felt unlikely to improve further. She continued to demonstrate problems with her memory, executive functioning, and ability to formulate plans. She was discharged to an assisted living arrangement. Her application for disability was pending.

Discussion

The patient described here showed significant cognitive impairment that may have been the result of mild COVID-19 infection, with an apparent delay from COVID-19 symptoms to the recognition of cognitive impairment. Although

the cause of her cognitive decline was felt most likely to be COVID-19, there are confounding factors that do not permit this to be concluded unequivocally.

Risk factors for severe COVID-19 infection overlap with risk factors for cognitive decline, including advanced age, medical comorbidities, hypertension, diabetes, obesity, and smoking. Thus, the highest risk individuals for severe infection may represent the most susceptible population for cognitive decline in the setting of COVID-19 infection [6]. Other risk factors for cognitive decline following COVID-19 infection include severity of lung affectation and potentially restricted oxygen delivery [10], neurological symptoms during infection, diarrhea, and the need for oxygen therapy [11]. Risks of neurological morbidity are greatest in, but not limited to, patients who had severe COVID-19 [12]. One previous study of 93 individuals (average age 62.6) who already had low MoCA scores (average 21.6 pre-pandemic) showed a further mild decrease of an average of about 1.4 points 6 months after mild COVID-19 infection [13]. However, this patient was more than 10 years younger, and her decline appeared to be much more severe relative to her reported premorbid functioning.

This patient had what would be considered a mild case of COVID-19 [14]. The fact that she never required oxygen therapy suggests that her respiratory symptoms were not significant. She had none of the risk factors noted above except for RA, which may present as CNS vasculitis, which is considered a medical comorbidity. Sedating medications ordered at the county hospital may have temporarily contributed to her impairment of cognition, but her overall impairment persisted well after their discontinuation and after she had become fully alert. Her abdominal pain could have been related to COVID-19, but all of her abdominal symptoms resolved quickly and completely after the cholecystectomy.

Although the hippocampus appears particularly vulnerable to coronavirus infections, COVID-19 infection may spread rapidly throughout the CNS [5], and sustained cognitive impairments might be a complication after recovery from COVID-19 regardless of clinical course [4]. It is important to be careful when attempting to distinguish between delirium, dementia, and psychosis in patients with altered mental status, because failure to do so can complicate timely diagnosis and treatment. Recognition of delirium is essential because leaving it untreated increases the risk of health complications. Patients with COVID-19 infection may have high rates of delirium [15], a manifestation of acute encephalopathy described by DSM-5 as a disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment); development over a short

period of time (usually hours to a few days), representing a change from baseline attention and awareness, and tending to fluctuate in severity during the course of a day; and an additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception) [16]. Some COVID-19 patients may ultimately also have symptoms of dementia that persist with decline in complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition domains. Psychosis with symptoms such as delusions or hallucinations may occur in the context of COVID-19 infection; however, this is uncommon [17].

The long-term effect of COVID-19 on cognitive functioning is becoming increasingly apparent, even in those with mild COVID-19 symptoms [6]. A significant number of cases may be associated with an executive dysfunction syndrome including attention control deficits and difficulties in planning, abstracting, behavioral control and orientation [18], and that appears to have been the case with the patient described here. It is unclear why she had an apparent delay from the COVID-19 symptoms to the recognition of cognitive impairment. To date, there is very little information in the literature about the chronological development of cognitive problems secondary to COVID-19. In the case of this patient, the latency might argue for a demyelinating or inflammatory process. Other clinicopathological states that could be involved in her presentation include clotting disorders and microvascular damage. Reports describing patients experiencing chronic symptoms after resolution of acute COVID-19 (long COVID) suggest a constellation of symptoms with similarities to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [19]. A hallmark of viruses linked to ME/CFS is the ability to establish persistent and chronic infection [20]. This phenomenon could have been a contributing factor with the patient described here. The need for monitoring and treatment for post-COVID-19 patients is evident.

Limitations of this case study include the fact that although this patient's cognitive impairment was likely due to COVID-19, this cannot be concluded unequivocally. A cerebrospinal fluid (CSF) autoimmune encephalitis panel was not done with the lumbar puncture at the regional hospital (possibly because of the normal CSF WBC). Thus, CNS vasculitis cannot be completely ruled out, although the normal CSF WBC lessens the likelihood of vasculitis. CT/MRI angiography could have helped clarify the diagnosis. The patient was not given a trial of steroids, so what effect steroids might have had on the patient's outcome is unknown. More detailed neurocognitive testing could also have been beneficial. Finally, the diagnosis is

not fully clear without a series of similarly affected patients to identify a syndrome.

Conclusions

This case report highlights the need for recognition of cognitive impairment in patients following COVID-19 infection, including those who had mild infections. As part of a holistic approach, osteopathic physicians could benefit this population by providing early recognition of cognitive impairment. Longitudinal studies will be necessary to ascertain the course of the development of cognitive impairment more clearly in patients with COVID-19 and what factors put certain patients at higher risk.

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