Cognitive Complications of COVID-19 Infection

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ABSTRACT

SARS-CoV-2 is associated with a post-infectious neurocognitive syndrome characterized by fatigue and deficits in attention, memory, and executive function. As screening cognitive testing generally remains normal, the pathophysiologic basis of these symptoms remains controversial and there is no standardized treatment paradigm. We present a clinical case demonstrative of typical neurocognitive sequelae of SARS-CoV-2 infection, highlighting medical and social factors that may have contributed to the severity of symptoms. We discuss the pathophysiologic evidence for cognitive "brain fog" following COVID-19 infection as well as lifestyle changes and rehabilitation strategies that may improve recovery. As the benefits of pharmacologic therapy remain unproven, we close with a brief discussion of medication options that might be appropriate targets for future clinical trials in the context of rehabilitative treatment.

KEYWORDS: Long COVID; PASC; brain fog; dysexecutive syndrome

CLINICAL CASE PRESENTATION

A 56-year-old woman with no significant medical history was infected by SARS-CoV-2 in October 2020, prior to the availability of commercial vaccinations. She experienced mild respiratory symptoms with loss of her sense of taste and smell, and then developed fatigue, difficulty concentrating, severe dyspnea on exertion, and exertional tachycardia. When these symptoms persisted for five months, she sought multidisciplinary care from infectious diseases, neurology, and cardiology specialists.

She had remained out of work because fatigue and cognitive symptoms limited her abilities and she was unable to meet the requirements of her demanding clerical job. She felt a general fogginess of mind, accompanied by forgetting details, trouble concentrating, and a remarkable difficulty with multitasking, which was well below her baseline. She also slept for long periods during the day but had difficulty remaining asleep at night and overall had poor sleep quality. She was unable to return to her regular exercise regimen due to her fatigue and exertional symptoms.

Her initial neurological evaluation revealed a perfect score (30/30) on the Mini-Mental Status Examination, a normal neurological examination without neglect or focal cognitive symptoms, and a normal electroencephalogram and magnetic resonance image (MRI) of the brain. She was treated conservatively, with recommendations to engage in intellectually stimulating activities and practice sustaining attention to specific tasks (in her case, meditation and yoga).

She attempted a gradual return to work, but failed to perform as required. During a particularly alarming episode, she could not recall the details of a conversation on the previous day, even with cueing. Due to her residual cognitive impairments six months following infection, she was referred for a formal neuropsychological evaluation.

In contrast to her normal performance on cognitive screening tests, her deficits on a neuropsychological test battery were striking. She had mild to moderate impairments in multiple domains, including attention, processing speed, executive control, fine motor dexterity, learning, and memory. However, these deficits were present only in a subset of tests of executive control within each cognitive domain. Notably, embedded measures of mood and effort showed no evidence of depression or intentional underperformance. She was diagnosed with a dysexecutive pattern of cognitive impairment and met criteria for mild neurocognitive disorder.

A trial of donepezil subjectively improved the cognitive symptoms, but without clear objective benefit. Her cardiac evaluation showed evidence of myocarditis and she underwent cardiac rehabilitation with a gradual return to her previous exercise tolerance and frequency. Ten months after her infection, she returned to work part-time but was able to perform at only 20% of her previous productivity level. She continued to work on sustaining attention to single tasks and avoided multitasking in order to complete her work duties.

Repeat neuropsychological testing a year later demonstrated improvements in executive aspects of attention and cognitive flexibility, but her memory and semantic fluency were unchanged. Seventeen months following her initial infection, she continued to meet neuropsychological criteria for mild neurocognitive disorder. She did not regain her sense of smell or taste. Her overall cognitive profile was consistent with the emerging literature on the Long COVID neurocognitive syndrome.

COGNITIVE SYMPTOMS FOLLOWING SARS-COV-2 INFECTION

The post-acute sequelae of SARS-CoV-2 infection (PASC) are a growing health crisis, estimated to currently impact 110,000 Rhode Island residents.[1] PASC is an umbrella term for multisystem involvement (pulmonary, cardiac, musculoskeletal, etc.) that persists longer than 4 weeks after the acute COVID-19 infection. This article focuses specifically on the cognitive PASC that cannot be readily explained by acute events during infection, such as global hypoxic injury or stroke.

Our patient provides a typical example of the neurocognitive syndrome associated with SARS-CoV-2 infection, and case series have consistently highlighted a range of deficits in executive function.[2,3] Here, executive function refers to the cognitive processes (e.g., organization and planning) that control our more basic cognitive functions.[4] Executive control is less important for routine or memorized behaviors but is critical when we are confronted with novel tasks, unfamiliar environments, or conflicting rules. These situations arise routinely in day-to-day human life.

Given the major influence of executive function over other cognitive domains, it follows that dysexecutive impairments can cause difficulties in attention, concentration, processing of new information, task selection and monitoring, and manipulation of working memory.[4] Multi-tasking is especially impaired, because the difficulty of each simultaneously performed task is effectively multiplied.[5]

Executive dysfunction is experienced uniquely by each patient. Some may present with a specific concern such as forgetfulness or trouble focusing and others with subtle global dysfunction that causes them to feel foggy or slow. The primary symptom is likely related to the cognitive domain that is most stressed in the patient's life. Function outside the home is likely to be more impaired than at home, where habits and routines can compensate.

Regarding the incidence of cognitive PASC, high quality prospective data are limited because many large studies only asked about fatigue, did not control for acute stroke or hypoxia, or had study design biases. Acknowledging these challenges, current estimates range from 7% to 54%,[6] with individual cohort rates as high as 81%.[7,8]

There are some studies of cohorts similar to our patient. A longitudinal prospective study[9] followed subjects who had premorbid cognitive, MRI, and EEG data, and excluded patients who were hospitalized, required oxygen, or developed new MRI lesions. Patients who became SARS-CoV-2 seropositive averaged a 2-point decline in their Montreal Cognitive Assessment (MOCA, maximum score 30) from baseline, and 21% experienced a loss of 4+ points, which met the criterion for measurable cognitive decline in this cohort.

Critically ill patients have higher rates of cognitive dysfunction following COVID-19, but this is proportional to their higher rates of stroke and other medical complications.[10] Some propose that critically ill patients may suffer from a concurrent post-ICU syndrome that is not unique to COVID-19,[11] creating a multifactorial cognitive disorder with complicated rehabilitation needs.

Unfortunately, the benefit of vaccination in preventing PASC is limited. In one review of VA medical records, vaccination was associated with only a 15% relative risk reduction of developing PASC following breakthrough infection, though sub-analysis verified protective benefit specifically against cognitive dysfunction.[10] Thus, even with widespread vaccination, a significant clinical population will experience cognitive changes following COVID-19 infection.

It remains to be seen whether emerging COVID-19 variants will be associated with similar rates of cognitive dysfunction. In population-level studies, the Omicron variant had half the incidence of PASC compared to the Delta variant,[12] but available studies do not distinguish cases on the basis of variant. Similarly, the link between neurological and other systemic manifestations of PASC is not well studied.

PATHOPHYSIOLOGY OF COGNITIVE SYMPTOMS

Even mild SARS-CoV-2 infection is associated with up to a 20% risk of developing dysexecutive cognitive impairment.[2,9] This is seen across multiple case series with varying disease severity,[13,14] cognitive assessment tools,[8] various cultural settings,[8,9,15,16] and age groups including the asymptomatic elderly.[17] We argue that it represents a distinct clinical entity with a physiologic basis that is under investigation.

There are ongoing efforts to explain how SARS-CoV-2 infection results in prolonged cognitive dysfunction. An inflammatory process is suspected,[18] whether from direct viral activity in the brain[19,20] or through a parainfectious process. The inflammation may be more prominent in limbic and frontomedial regions of the brain, as they are closer to the olfactory epithelium.[21–23] The pathophysiologic process involves endothelial disruption,[24] microglial activation,[19] neurotransmitter depletion,[25] and microvascular compromise.[26] This process appears to cause leukoencephalopathy[27] and accelerated focal and global cortical atrophy,[21] with resultant network dysfunction and cognitive changes.

No studies provide strong evidence for using anti-viral or anti-inflammatory medications to prevent or treat cognitive PASC. As the NIH COVID-19 Treatment Guidelines Panel does not recommend steroid therapy for patients that do not require oxygen support,[28] any retrospective study would likely be confounded by differences in disease severity or degree of hypoxia. This remains an avenue for further clinical investigation.

CLINICAL MANAGEMENT OF COGNITIVE PASC

As there is no established treatment regimen, the management of cognitive symptoms following SARS-CoV-2

infection focuses on supportive care and the identification and treatment of other confounding medical factors. A high index of suspicion is necessary to recognize the dysexecutive pattern typical for neurocognitive PASC. This syndrome may present as a specific cognitive concern, as generalized fogginess or trouble with concentration or memory, or as difficulty at work or in community activities. Generally, elderly people and those with premorbid intellectual or cognitive disability are disproportionately affected.

Inappropriate behavior or violations of social norms should raise concern for alternative frontal lobe pathology. Similarly, a patient showing progressive declines over time should raise concern for an underlying degenerative process versus another comorbid risk factor for cognitive impairment. It is also possible that cognitive PASC could be superimposed on premorbid neurological conditions.

Patients should undergo a thorough screening for alternative causes of cognitive dysfunction, including a basic metabolic panel, complete blood count, vitamin B-12 and folic acid levels, thyroid function tests, a routine non-contrasted MRI of the brain, and other tests guided by the clinical picture. A relatively normal brain MRI is expected and structural lesions should prompt pursuit of alternative diagnoses such as ischemic stroke or frontal lobe tumor. If leukoaraiosis or ischemic white matter disease is detected, then aggressive control of microvascular risk factors should be initiated, with screening for hypertension, diabetes, and hyperlipidemia. Any comorbid mood or sleep disorders (e.g., depression or sleep apnea) that may contribute to poor cognitive performance should also be addressed.

If the initial diagnostic workup is reassuring, we recommend a period of symptom monitoring with a patient-directed cognitive rehabilitation regimen. Lifestyle changes for improved brain health include intellectually stimulating activities, community engagement, good sleep quality, smoking cessation, avoidance of mind-altering substances such as marijuana and alcohol, regular exercise, and a healthy diet.

A core challenge in the dysexecutive syndrome is that difficulties with attention and working memory often leads to a marked loss of the ability to multitask. To compensate for this, we recommend activities that allow focusing on a single task or thought process for progressively longer periods of time. In this manner, one can complete a series of tasks efficiently, allowing progression through a list and achieving a level of productivity that is similar to multitasking. In our case, yoga and meditation were recommended; however, one may find similar benefits in other exercises or outdoor activities, a game or puzzle, an art or crafting activity, reading a book, or enjoying music. In contrast, television or video media can impair sustained attention due to frequent scene changes and distracting elements.[29] This approach is similar to the strategies for improving executive functioning following traumatic brain injury.

There have been mixed reports regarding the potential for COVID-19 vaccination after acute infection to improve PASC symptoms.[30] Vaccination appears to be safe and does not worsen symptoms or quality of life.[31] Given the possibility of reinfection (and further cognitive insults) and the modest but measurable protection that vaccination offers, we recommend full vaccination with booster doses following CDC guidelines if the patient has not undergone it.

Regarding medical management of PASC, there are no available clinical trials to support the use of any particular pharmacotherapy. In the acute phase, selected sigma-1 receptor modulating antidepressants (e.g., fluvoxamine) have been postulated to have a neuroprotective role,[32] but this has not translated into a treatment recommendation for acute or post-acute care. Case reports, such as in this article, do not demonstrate clear and consistent benefits, and the side effects of cognitive stimulants can be significant.

Further pharmacologic insights might be gleaned from a related condition that is often compared to the post-COVID brain fog, that of chemotherapy-induced cognitive impairment. The effects of various classes of cognitive enhancers have been reviewed in this context.[33] In general, results were promising in small and carefully selected patient cohorts, often with preexisting cognitive difficulties. Clinical trials are ongoing, and no general treatment recommendation can be made at this time.

Given the lack of high-quality clinical data and the concern for side effects and adverse cognitive changes, we do not recommend routine pharmacotherapy in the management of cognitive PASC.

In the absence of alternative pathology, we recommend symptom monitoring, lifestyle optimization, and attention training for a period of six months. If symptoms persist at that time, we obtain formal neuropsychological testing for a baseline measure of cognition; determine the likelihood of alternative pathologies; and select targeted interventions with the assistance of occupational or speech and language therapists. A formal neurological evaluation should be considered for any patient who does not present with typical symptoms, has ongoing progression of symptoms following the acute infection, or has focal examination or imaging findings.

CONCLUSION

Mild SARS-CoV-2 infection is associated with a prolonged neurocognitive syndrome of impaired executive function in as many as 20% of cases. The chief complaint and major symptoms expressed may vary between patients as a function of their premorbid status and lifestyle. There is no recommended pharmacotherapy at this time, and treatment focuses on establishing an individualized cognitive rehabilitation regimen and excluding or treating other comorbid conditions that may impair cognition.

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