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Neurocognitive Sequelae following COVID-19 Infection in Older Adults with and Without Pre-Infection Neurocognitive Impairment

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Abstract

In this case report, we describe the clinical characteristics of three older adults aged >65 years with cognitive difficulties prior to their COVID-19 infection who reported worsening of neurocognitive symptoms in the convalescent COVID-19 phase. Formal neuropsychological testing along with neuroimaging were included with each patient. These patients described an initial worsening in cognitive function after recovering from the acute phase of COVID-19. This case report describes variable recovery of cognitive abilities in the convalescent stage. The direct effect of the viral infection itself on cognitive function are well documented. We hypothesize that the persistent inflammatory or immune response in the convalescent COVID-19 stage, more commonly referred to as the indirect mechanism, contributes to the clinical syndrome known as the Post-Acute Sequelae of SARS-CoV-2 (PASC).

Keywords: *SARS-CoV-2, COVID-19, coronavirus, cognition, neurocognitive, convalescence, PASC*

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS- CoV-2) infection has been associated with significant morbidity and mortality [1]. During the acute infection period, reported central nervous system (CNS) involvement has ranged from acute delirium to meningoencephalitis [2-5]. While these acute neurological symptoms and manifestations have been well-described, the long-term cognitive and neurobehavioral outcomes have yet to be fully characterized in older adult convalescent coronavirus disease (COVID-19) patients [1], particularly in those with pre-existing cognitive impairment. Although about 70-80% of infected individuals recover uneventfully without lasting impairment or complications [6], the remainder develop long-COVID also termed Post-Acute Sequelae of SARS- CoV-2 (PASC) with symptoms lasting 12 weeks or more [7-9], that has been attributed to chronic inflammation with immune activation and dysregulation [10,11].

Characterizing the neuropsychiatric phenotype of older adult COVID-19 patients during their convalescent period is particularly important, especially those with lingering or worsening symptoms, since the relationship between SARS-CoV-2 infection and cognitive dysfunction remains unclear.

This case report describes the clinical characteristics of three older adults (aged > 65 years) who reported worsening neuropsychiatric symptoms in the SARS-CoV-2 convalescent period. Specifically, we report neuroimaging and neuropsychological testing information, which may provide supporting evidence for indirect effects of chronic inflammation following COVID-19 on the brain [10,11] in contrast to direct evidence such as acute response to a viral load. Differing clinical characteristics in the patients reported here suggest that long-term

neuropsychiatric symptoms in COVID-19 patients are likely multifactorial, reflecting a combination of residual neurological involvement due to a direct (acute response to viral infection) or indirect (chronic inflammatory response with immune activation and dysregulation) mechanisms [10,11].

Methods

Three older adults (>65 years) who noted worsening cognitive difficulties after SARS-CoV-2 infection were evaluated in the Memory Clinic of the Duke Neurological Disorders Clinic.

Electronic medical records were retrospectively reviewed. Examination included a comprehensive neurological evaluation with cognitive screening using the Montreal Cognitive Assessment (MoCA), clinical neuroimaging, and a subsequent formal neuropsychological evaluation. Prior patient history and data were collected for comparison with the post-COVID-19 clinical evaluation profiles.

Results

Patient 1 is a 69-year-old male with a high school education and a history of diabetes, hypertension, depression, and a first-order relative and maternal aunt with late-onset Alzheimer's disease dementia who presented for evaluation of memory loss. The memory loss had been ongoing for about one year but had significantly worsened in the five months following his recovery from COVID-19. He had documented antibodies against SARS-CoV-2.

At that time, no vaccine was available. The patient reported that he can no longer remember when he had eaten, and evinced navigation issues when driving on familiar roads. Prior to SARS-CoV-2 infection, head computed tomography (CT) without contrast revealed mild bilateral hippocampal atrophy. The patient demonstrated a score of 16 on the Functional Activities Questionnaire (FAQ), 4/8 on AD8 Dementia Screening, 1 on Neuropsychiatric Inventory (NPI), and 20/30 on the MoCA (Table 1). Geriatric Depression Scale (GDS) score was 4, Patient Health Questionnaire-9 (PHQ-9) was 10, General Anxiety Disorder-7 (GAD7) was 0, and Epworth Sleepiness Scale (ESS) was 11. Neuroimaging was not repeated. Formal neuropsychological evaluation (Table 2) was performed five months after recovery from active COVID-19 infection. With premorbid cognitive abilities estimated to be below-average, neurocognitive assessment measure results revealed isolated difficulties in executive task performance and diminished acquisition and impaired un-cued retrieval on memory assessment measures. Performances on measures of attention and executive function were in the low average to average range on a majority of tests, which is in keeping with the patient's premorbid ability estimates.

Table 1: National Alzheimer's Coordinating Center (NACC) Montreal Cognitive Assessment (MoCA) Subdomain Index Performance Scores.

	Index Scores						
Patient	***MoCA Score***	***Executive***	***Attention Concentration***	***Language***	***Visuospatial***	***Orientation***	***Memory***
1	*20*	*9*	*7*	*4*	*6*	*4*	*2*
2	*27*	*13*	*10*	*6*	*7*	*2*	*2*
3 (2020)	*22*	*11*	*7*	*3*	*6*	*6*	*1*
3 (2021)	*23*	*9*	*8*	*5*	*7*	*6*	*2*

He did display below average abilities for verbal reasoning and complex attention (working memory), and he was proneto errors and perseveration during a problem-solving test. Visual-spatial abilities were commensurate with premorbid estimates. Language abilities were low average for phonemic fluency, but more markedly impaired for semantic fluency, suggesting possible reduction in elaboration of semantic knowledge stores. Confrontational object naming was low average. In terms of memory, acquisition and retrieval of rote verbal information were borderline, suggesting a weakness in learning and recall.

Retention was 63% and although his recognition memory score was low, he recognized previously learned items. Performance improved on a measure of contextual verbal memory, with learning and recall commensurate with premorbid ability. Visual memory was attenuated for learning and impaired for recall, although he did have normal recognition memory for this visual information. The patient denied mood symptoms on a self-report measurement. These findings indicated frontal/subcortical system dysfunction (Table 2). Other comorbidities included a history of vitamin B12 deficiency treated with B12 injections, atrial fibrillation, congestive heart failure, chronic obstructive pulmonary disease, obstructive sleep apnea, and morbid obesity. A diagnosis of late-

onset Alzheimer's disease (AD) without behavioral disturbance was assigned in this case, and the patient was started on donepezil.

Patient 2 is a 68-year-old male with a Master's degree

Table 2: Demographics and Formal Neuropsychological Evaluations

Demographics	Case 1	Case 2	Case 3
Age (years)	69	69	73
Sex	Male	Male	Male
Education	12	18	16
Race	White	White	Black
Tests			
TOPF	37	61	41
Intellectual Functioning			
WAIS-IVGAI	33	67	46
VCI	30	71	47
PRI	38	60	44
Executive Functioning			
TMT A	48	31	33
TMT B	39	42	42
WCST Categories (Raw)	1	NA	1
Digit Span	30	50	37
Coding	37	42	32
Language			
BNT	38	56	33
FAS	37	49	41
Animal	28	48	44
Vocabulary	33	55	50
Similarities	33	67	67
Verbal Memory			
HVLT Total Learning	35	50	33
HVLT Delayed Recall	36	44	≤ 20
WMS-IV Logical Memory I	47	52	55
WMS-IV Logical Memory II	40	54	59
Visual Memory			
BVMT Total Learning	32	60	45
BVMT Delayed Recall	24	63	46
Mood			
GDS (Raw)	5	8	3

NA = Not administered; All scores are T scores (mean of 50, SDof 10) unless indicated.

TOPF = Test of Premorbid Functioning; WAIS = Wechsler Adult Intelligence Scale; GAI = General Ability Index; VCI = Verbal Comprehension Index; PRI = Perceptual Reasoning Index; TMT = Trail Making Test; WCST = Wisconsin Card Sorting Test; BNT = Boston Naming Test; FAS = phonemic fluency using letters; HVLT = Hopkins Verbal Learning Test; WMS = Wechsler Memory Scale; BVMT = Brief Visuospatial Memory Test; GDS = Geriatric Depression Scale.

and a history of anxiety, depression, and attention deficit disorder (ADHD) who presented four months after recovering from COVID-19 for evaluation of poor memory, inability to "visually map," and daily "senior moments" as wellas a prolonged period of confusion while driving. He had documented antibodies to SARS-CoV-2 prior to vaccine availability. He had transient memory problems two years prior that improved after changing his anti-depressant medication (bupropion) dosage. After recovering from his COVID-19 infection, the patient began to regularly misplace objects and often stop a task midway

through, thinking he had completed it. There was no family history of cognitive impairment. Head CT was unremarkable. MRI of the brain demonstrated mild hippocampal and biparietal lobe atrophy, as well as mild cerebral white matter disease. He scored 7/8on the AD8 Dementia Screening and 27/30 on the MoCA (Table 1). PHQ-9 was 9, GDS was 2, GAD7 was 16, and NPI was 7. B12 was normal.

Formal neuropsychological evaluation (Table 2) was completed six months after recovery from COVID-19 infection. With premorbid cognitive abilities estimated to be above- average, formal neuropsychological testing revealed only a few notable findings, which included a reduction in speeded task performance in areas of simple and complex sequencing and basic processing speed. Other areas of testing were average or better than average. These findings were thought to reflect some degree of frontal or subcortical system involvement. Recognizing some evidence of neurocognitive recovery, a diagnosis of subjective cognitive impairment (SCI) - thought to be related to multiple factors, including pre-existing ADHD, mild microvascular ischemia, and history of mood symptoms – was made.

Patient 3 is a 73-year-old male with a bachelor's degree and a history of apolipoprotein E (ApoE) genotype of ε3/ε3 and a history of sleep apnea, multinodular goiter, aortic aneurysm, and hypercholesterolemia. He has two brothers, each diagnosed with an unspecified dementia. Prior to contracting COVID-19, he presented to the Duke Memory Disorders clinic for evaluation of memory difficulties, episodes of confusion, misplacement of belongings, and difficulty remembering driving routes. At that time, his global cognitive screening MoCA score was 22/30, reflecting possible mild cognitive impairment (MCI) difficulties (Table 1). Other neurocognitive and psychiatric screening data reinforced the likelihood of MCI, but with general preservation of functional abilities with an AD8 of 3/8 and FAQ of 1. His psychiatric screening data were largely devoid of any self-reported anxiety or depression symptoms with an NPI of 1, GDS of 0, GAD7 of 0, and PHQ-9 of 1.

Volumetric neuroimaging (MRI - T1 spoiled gradient echo [SPGR] sequence) failed to demonstrate any appreciable regional mesial temporal lobe or global atrophy patterns. On T2 weighted imaging, he was found to have patchy T2 white matter hyperintensities within the periventricular and deep white matter, likely reflective of mild chronic ischemic microvascular disease without a specific etiology to explain his cognitive symptoms (Figure 1A). NeuroQuant® (CorTech Labs, San Diego, California) analysis estimated bilateral hippocampal volume at 95% for age (Figure 1B).

He received a pre-SARS-CoV-2 infection diagnosis of MCI. Approximately 12 months later, prior to vaccine availability, he was hospitalized with COVID-19 after testing positive for SARS-CoV-2 by polymerase chain reaction (PCR). His condition was complicated by acute delirium with transient disorientation and viral pneumonia. After fully recovering from the SARS-CoV-2 infection, he noted an increase in subjective memory difficulties over the ensuing months compared to his pre-infection baseline. An evaluation determined that he was fully independent for all basic and advanced activities of daily living (ADL). His post-COVID-19 global cognitive screening MoCA score was 23/30, possibly reflecting either stable or slightly improved overall cognition (Table 1). Additional cognitive screening data were consistent with general stability with an AD8 of 3/8. Even though significant changes in functioning were subjectively gauged by the patient (FAQ = 10) relative to his pre-infection baseline (FAQ =1), he remained fully independent on all ADLs. His subjective mood symptom screening results slightly worsened, although remained non-diagnostic for clinically significant mood disorder with an NPI of 2, GDS of 3, GAD7 of 0, and PHQ-9 of 2. Formal neuropsychological evaluation (Table 2) completed 10 months after recovery from COVID-19 infection revealed that performances on measures of

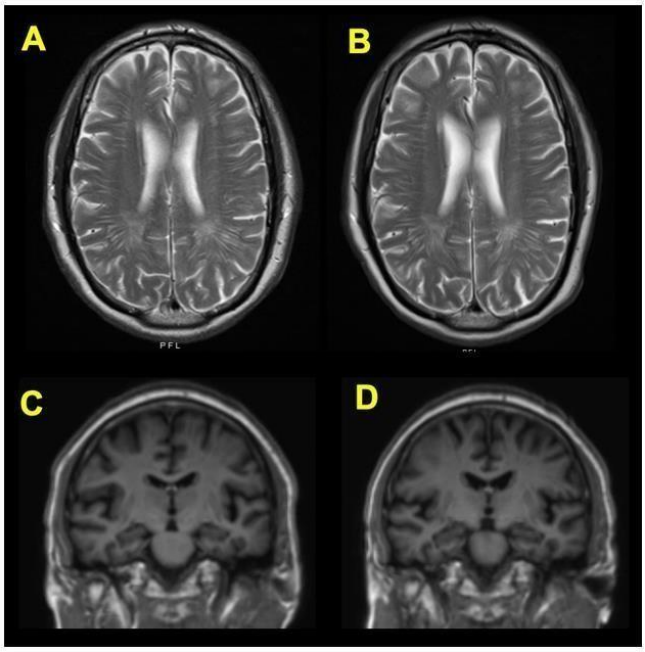

Fig 1. In axial T2 weighted MRI images, the periventricular white matter hyperintensities are unchanged and consistentwith age both before (A) and two weeks after the positive COVID-19 diagnosis (B). In T1 spoiled gradient echo (SPGR) MRI images, the hippocampal volume is similarly unaffected, both before (C) and two weeks after the positive COVID-19 diagnosis (D).

attention and executive function were within expectation for reasoning skills. There was at least mild attenuation in other aspects of executive function, including simple and complex sequencing, processing speed, attention, and problem-solving. General visual-spatial abilities were intact. Phonemic fluency was low average and object naming was weak, in the borderline range. In terms of memory, acquisition of rote verbal information was weak, in the borderline range, and delayed recall was impaired, with 0% retention of learned information. Although recognition discrimination was weak compared to same age peers, it appeared that he recognized items previously learned. Otherwise, memory performances on an additional verbal task and visual task were normal. He denied mood symptoms on a self-reported measure. Thus, results on this neuropsychological evaluation revealed difficulties in certain aspects of executive function, particularly for timed and complex tasks. This impacted executive aspects of additional testing areas including more difficulty on a memory test with higher executive demand and attenuated phonemic fluency. These findings suggested frontal and subcortical system involvement, consistent with imaging evidence of microvascular ischemic change. Deficits in semantic language/confrontational naming was thought to be due to left temporal involvement**.** There was no indication of medial temporal involvement and thus the consensus was that there was no amnestic component. In direct comparison with his pre-COVID neuroimaging data (Figures 1A, 1C), post-infection and recovery demonstrated that the patchy hyperintensities within the periventricular and deep white matter remained unchanged and nonspecific (Figure 1B). Neuro Quant analysis revealed that hippocampal occupancy remained within normal limits (95% of normal) (Figure 1D). He was diagnosed with mild neurocognitive disorder and non-amnestic MCI without behavioral disturbance.

Discussion

This case report describes the potential exacerbation and progression of pre-existing cognitive difficulties after recovery from acute COVID-19 infection in three older adults who completed formal neuropsychological evaluation. The early PASC period in these individuals resulted in diagnoses that spanned much of the cognitive spectrum which included SCI, MCI, and AD. Longitudinal investigation of convalescent patients is necessary to allow better characterization and insight into the long-term neurological effects of COVID-19 infection. Additionally, a longitudinal study may provide insight into the likely immune and inflammatory mechanisms that have been postulated to lead to PASC [10,11].

Other potential contributory etiologies such as the effect of comorbid conditions, a lengthy hospitalization, intensive care stays, intubation, oxygen levels, and even education level may be better understood through longitudinal investigation.

The acute symptoms of COVID-19 are now well documented [1]; however, there is currently a gap in knowledge regarding the long-term neurological consequences following COVID-19 infection, particularly the neuropsychiatric sequelae [12] in those who manifest persistent inflammation and immune responses that characterize PASC [10,11]. Several case reports of COVID- 19-related changes in mental status have correlated the clinical symptoms with significantly elevated CNS inflammatory markers [13-16]. Intriguingly, neuroinflammation is a key contributor to AD pathogenesis in humans [17]. Such an inflammatory response, hypothesized to contribute to AD, is increasingly appreciated for its capacity to exaggerate downstream impairments in cognitive function; therefore, characterization of the inflammatory response using both fluid and imaging biomarkers are critical to provide insight into the development of mental status changes in COVID-19 patients as well as in those who develop PASC. The cases presented herein demonstrate a worsening clinical trajectory in those already at risk for progression of neurodegenerative disease directly following infection with SARS-CoV-2, with patient 1 continuing to worsen. Over time, however, Patient 2 begins to show some improvement, and Patient 3 exhibits a more stable clinical trajectory. This case report highlights the importance of better understanding through larger, longitudinal studies why some patients are able to recover while others develop PASC. Data collected from previous coronavirus outbreaks, including 2002 SARS-CoV and 2012 MERS-CoV, have demonstrated evidence of long-term behavioral health outcomes such as depression, anxiety, fatigue, and post-traumatic stress disorder, as well as rarer neuropsychiatric syndromes [15,18]. Other neurologic and psychiatric conditions, such as encephalopathy, neuromuscular dysfunction, demyelinating processes, and impaired memory and psychosis, may also follow viral infections [12,18].

The incidence and prevalence of such neurological outcomes following COVID-19 are still being explored [18,19]. A retrospective cohort study from the United Kingdom (UK) studied over 236,000 COVID-19

patients and concluded that in the 6 months post-infection, just over 10% with no prior history of neurologic or psychiatric disease developed such an ailment, whereas 1/3 with prior history received a diagnosis [18]. Mood disorders and anxiety were more common (31%) than neurologic disorders (3.5%). The progressive memory loss in patient 1 soon after recovery from COVID-19 highlights the ability of SARS-CoV-2 to adversely affect cognition in an individual with pre-existing memory difficulties.

Individuals at a higher genetic risk of developing AD-related dementia (ADRD) are xperiencing a higher risk of severe COVID-19; the risk of severe COVID-19 for people carrying two ApoE ε4 alleles is doubled (OR = 2.31) compared with the more common ApoE ε3ε3 genotype [15,20] as in patient 3. Though Patient 3 carried no ε4 alleles, his pre- COVID-19 diagnosis placed him within an at-risk category along the ADRD continuum [20]. Although available studies have described memory loss, confusion, and dementia-like manifestations as a component of acute infection [22,23], our cases illustrate progression along the Alzheimer's continuum early in the COVID-19 convalescent period. The immediacy of this threat further underscores the importance of closely following older adult convalescent COVID-19 patients given the broad clinical phenotype of PASC that is now evident from extended follow-up in neurology-based and psychiatry-based clinics. Given the large number of infected individuals during this worldwide pandemic, these long-term neurocognitive effects on the human condition may be more significant and far-reaching than have been realized thus far. Although this small case report of 3 male patients without extended follow-up may be limited by potential retrospective and attribution biases, the findings support the need for longitudinal investigation of convalescent patients in a controlled setting. Other external contributing factors that may affect cognition, mood, and anxiety should also be considered and better understood in individuals with PASC. Such work will help further characterize these observations and provide insight into their pathophysiology as we strive to understand the long- term neurocognitive and psychiatric effects of SARS-CoV-2 in infected individuals. Following recovery from the direct insult of active COVID-19 disease, chronic inflammation with immune activation and dysregulation in PASC [10,11] may result in a more rapid and progressive neurocognitive trajectory in some individuals with comorbid neuropsychiatric disorders or in those who are at risk for developing such. Larger longitudinal studies are needed to further characterize these observations.

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None.

Conflict of Interest

There are no conflicts of interest to disclose.

Declaration of Interest

The authors report that there are no financial or non-financial competing interests to declare.

Data Availability Statement

All relevant data was included in the submitted manuscript. Other data may be available only on request due to privacy/ethical restrictions since this information contains Protected Health Information (PHI). Each patient included in this manuscript signed a Consent-To-Publish form. Thus, the data that support the findings of this study are available on request from the

corresponding author [AJL]. Other than what has been included in this manuscript submission, the data are otherwise not publicly available due to their containing information that could compromise the privacy of research participants.

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