Journal of Alzheimer's Disease Reports 7 (2023) 119–128
DOI 10.3233/ADR-220090
IOS Press

Research Report

The Effects of SARS-CoV-2 Infection on the Cognitive Functioning of Patients with Pre-Existing Dementia

Souvik Dubey[a], Shambaditya Das[a], Ritwik Ghosh[b], Mahua Jana Dubey[c], Arka Prava Chakraborty[a], Dipayan Roy[d,e,f], Gautam Das[a], Ajitava Dutta[a], Arindam Santra[a], Samya Sengupta[g] and Julián Benito-León[h,i,j,*]

[a]*Department of Neuromedicine, Bangur Institute of Neurosciences (BIN), Kolkata, West Bengal, India*
[b]*Department of General Medicine, Burdwan Medical College, and Hospital, Burdwan, West Bengal, India*
[c]*Department of Psychiatry, Berhampur Mental Hospital, Berhampur, West Bengal, India*
[d]*Department of Biochemistry, All India Institute of Medical Sciences (AIIMS), Patna, Bihar, India*
[e]*Indian Institute of Technology (IIT), Madras, Tamil Nadu, India*
[f]*School of Sciences, Indira Gandhi National Open University, New Delhi, India*
[g]*Department of General Medicine, Apollo Gleneagles Hospital, Kolkata, West Bengal, India*
[h]*Department of Neurology, University Hospital "12 de Octubre", Madrid, Spain*
[i]*Centro de Investigación Biomédica en Red Sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain*
[j]*Department of Medicine, Complutense University, Madrid, Spain*

Handling Associate Editor: Jesus Ávila

Received 6 November 2022
Accepted 3 January 2023
Pre-press 2 February 2023
Published 14 February 2023

Abstract.
Background: Cognitive postscripts of COVID-19, codenamed as 'cognitive COVID' or 'brain fog,' characterized by multidomain cognitive impairments, are now being reckoned as the most devastating sequelae of COVID-19. However, the impact on the already demented brain has not been studied.
Objective: We aimed to assess the cognitive functioning and neuroimaging following SARS-CoV-2 infection in patients with pre-existing dementia.
Methods: Fourteen COVID-19 survivors with pre-existing dementia (four with Alzheimer's disease, five with vascular dementia, three with Parkinson's disease dementia, and two with the behavioral variant of frontotemporal dementia) were recruited. All these patients had detailed cognitive and neuroimaging evaluations within three months before suffering from COVID-19 and one year later.

*Correspondence to: Dr. Julián Benito-León, Department of Neurology, University Hospital "12 de Octubre", Madrid, Spain. E-mail: jbenitol67@gmail.com.

ISSN 2542-4823

Results: Of the 14 patients, ten required hospitalization. All developed or increased white matter hyperintensities that mimicked multiple sclerosis and small vessel disease. There was a significant increase in fatigue ($p = 0.001$) and depression ($p = 0.016$) scores following COVID-19. The mean Frontal Assessment Battery ($p < 0.001$) and Addenbrooke's Cognitive Examination ($p = 0.001$) scores also significantly worsened.

Conclusion: The rapid progression of dementia, the addition of further impairments/deterioration of cognitive abilities, and the increase or new appearance of white matter lesion burden suggest that previously compromised brains have little defense to withstand a new insult (i.e., 'second hit' like infection/dysregulated immune response, and inflammation). 'Brain fog' is an ambiguous terminology without specific attribution to the spectrum of post-COVID-19 cognitive sequelae. We propose a new codename, i.e. 'FADE-IN MEMORY' (i.e., Fatigue, decreased Fluency, Attention deficit, Depression, Executive dysfunction, slowed INformation processing speed, and subcortical MEMORY impairment).

Keywords: Cognitive impairment, COVID-19, dementia, post-COVID-19

INTRODUCTION

Cognitive problems after COVID-19, codenamed as 'cognitive COVID' or 'brain fog', characterized by multidomain cognitive impairments, are now being reckoned as the most devastating sequelae of this disease [1–4]. Studies so far showed decreased attention and concentration, executive dysfunction, memory impairment, and delay in information processing speed dominate this clinical scenario [5–7]. Most cognitive post-COVID-19 studies have been performed on previously healthy individuals without any cognitive impairment prior to the COVID-19 infection [8–14]. Senescence, 'long COVID', prolonged hospital stay, need for ventilator support, high-flow oxygen therapy, and cytokine storm have been considered potential risk factors in isolation or combination for post-COVID-19 cognitive impairment across different studies [15–26]. Multifaceted plausible biological mechanisms underlying these cognitive symptoms have been proposed, i.e. immune dysregulation, ongoing systemic inflammation stemming from autoimmunity, direct viral invasion through the disrupted blood-brain barrier, and cerebral micro-hemorrhages [15–24]. Social stigma, isolation, loneliness, fear, panic, and inactivity contribute to post-COVID-19 cognitive impairment [4, 17, 27–31].

Several studies unraveled fatigue and cognitive impairment as the two most important post-COVID-19 neurological aftermath [18–21, 27, 28, 32]. Studies so far are consistent with white matter intensity changes in patients with post-COVID-19 cognitive impairment [33–37]. Numerous proposals are in the pipeline; however, the primary mechanism(s) of post-COVID-19 fatigue is/are still enigmatic. Researchers have mostly pointed toward cytokine and endocrine influences without much objective evidence [15–32]. Depression, albeit a primary psychiatric disease, is a post-COVID-19 burden associated with cognitive impairment, forcing researchers to rethink possible common neurobiological basis intertwining depression and post-COVID-19 cognitive impairment [15–32].

Post-COVID-19 rapid deterioration of cognitive abilities has been observed in previously cognitively intact people [8–14]. However, the impact on the already demented brain has not been studied. We aimed 1) to assess the cognitive functioning and neuroimaging following SARS-CoV-2 infection in patients with pre-existing dementia; 2) to search for underlying risk factors, pathophysiological basis, and possible central nervous system localization-related neurobiological association; and 3) to search for the missing thread unifying post-COVID-19 depression and fatigue with ensuing cognitive impairment.

MATERIALS AND METHODS

Out of a total of 550 patients with dementia who attended the wards of the Burdwan Medical College and Hospital (Neurology Superspecialty and Internal Medicine Wings), Bangur Institute of Neurosciences, and private cognitive specialty clinics, in West Bengal, India, between May 2013 and September 2022, we had the opportunity to recruit 14 COVID-19 survivors (nine men and five women) with a detailed neuropsychological and neuroimaging assessment within three months before suffering from COVID-19 and one year later. Four of them were previously diagnosed with Alzheimer's disease [38, 39], five with vascular dementia (defined as

dementia in conjunction with signs of focal neurological signs on clinical examination, evidence of relevant cerebrovascular disease on brain imaging, and either of onset of dementia within three months of a documented stroke or abrupt onset of cognitive impairment or step-wise/fluctuating deterioration of cognitive impairment) [40], three with Parkinson's disease dementia [41], and two with the behavioral variant of frontotemporal dementia [42].

Cognitive functioning was performed through Addenbrooke's Cognitive Examination III (ACE-III) [43], Frontal Assessment Battery [44], and the Trail Making Test Part B [45]. Attention, language, memory, visuospatial and fluency scores according to ACE-III [43] were taken thoroughly and analyzed to compare individual domain scores pre-COVID-19 and post-COVID-19. A gross comparative assessment of cognitive domain scores was calculated using the percentage of reduction of individual scores of each domain total score of ACE-III assessment pre- and post-COVID-19. The clinical dementia rating (CDR) scale [46] was also applied to our cohort pre and post-COVID-19. We used the fatigue severity scale [47] and two first items of the nine-item Patient Health Questionnaire [48] to measure fatigue and depression, respectively.

Brain magnetic resonance (MRI) (acquired with a Siemens Verio 1.5-T MRI scanner) was performed in all patients before COVID-19 and one year later. MRI was interpreted meticulously by three consultant radiologists with a comparison of pre and post-COVID-19 imaging findings. The Fazekas scale was used to quantify the amount of white matter T2 hyperintense lesions [49], and the Global Cortical Atrophy scale for cortical atrophy [50].

Statistical analyses

Routine descriptive statistics summarized data, namely mean and standard deviation (SD) for numerical variables that were normally distributed, the median and inter-quartile range for skewed numerical variables, and counts and percentages for categorical variables. Numerical variables were compared between the same groups at different times by paired *t*-test. McNemar test [51] was employed for comparisons of nominal data, and the Wilcoxon rank sum test [52] for ordinal data of the same group at different times. Analyses were two-tailed, and a statistical significance level was set at $p < 0.05$ for all comparisons. Statistical analyses were performed in SPSS Version 25.0 (SPSS, Inc., Chicago, IL).

RESULTS

The results are summarized in Tables 1 to 3. During COVID-19, ten of the 14 patients required hospitalization, but none had a stroke. The mean age of our cohort was 65.6 ± 5.02 years (mean $\pm$ SD). The mean age of patients with pre-existing Alzheimer's disease, Parkinson's disease dementia, frontotemporal dementia, and vascular dementia were 66.5 ± 2.89 years, 68.0 ± 6.00 years, 56.5 ± 2.12 years, and 67.2 ± 2.59 years respectively. There was a significant increase in fatigue ($p = 0.001$) and depression ($p = 0.016$) scores following COVID-19. The mean Frontal Assessment Battery ($p < 0.001$), ACE-III ($p = 0.001$), and CDR scale ($p = 0.002$) scores significantly worsened. Specifically, the worsening was seen in attention ($p = 0.019$), memory ($p < 0.001$), fluency ($p = 0.006$), language ($p < 0.001$), and visuospatial ($p < 0.001$) domains. Executive functions assessed by the Clock-Drawing test ($p = 0.021$) and the Trail-Making Test Part B ($p = 0.016$) also deteriorated significantly. There were a significant increase of periventricular white matter ($p = 0.002$) and deep white matter hyperintensities ($p = 0.001$), and global cortical atrophy ($p = 0.025$) on neuroimaging following COVID-19 infection in the follow-up period.

DISCUSSION

The most noteworthy observation was that all 14 (i.e.,100%) patients, one year after SARS-CoV-2 infection, had fatigue, depression, objective attention/concentration difficulties, executive dysfunctions, slowed information processing speed, and sub-cortical type memory impairments, irrespective of their previous cognitive status. Patients with a previous deficit in those domains scored poorer in post-COVID-19 assessment than in other domains. Fluency deteriorated significantly following COVID-19. Slowly progressive dementias like Alzheimer's disease and vascular dementia, which usually have a fluctuating course, showed relatively unusual significant, relentless, and rapid progression in terms of deterioration of total ACE-III score at one year post-COVID-19.

The spectrum of cognitive domain involvement followed a specific pattern, which indicates underlying disruption of frontal sub-cortical networks/connections. Fatigability/fatigue is a predominant symptom in multiple sclerosis (MS) and has

Table 1
Baseline demographic and clinical profile prior to COVID-19

	Whole cohort ($n = 14$)	Alzheimer's disease ($n = 4$)	Parkinson's disease dementia ($n = 3$)	Behavioral variant of frontotemporal dementia ($n = 2$)	Vascular dementia ($n = 5$)
Sex (Men: Women)	9 : 5	3 : 1	1 : 2	1 : 1	4 : 1
Age (y)	65.6 ± 5.02	66.5 ± 2.89	68.0 ± 6.00	56.5 ± 2.12	67.2 ± 2.59
Presence of vascular risk factors	57.1%	25.0%	33.3%	50.0%	100%

Table 2
Characteristics of COVID-19

	Whole cohort ($n = 14$)	Alzheimer's disease ($n = 4$)	Parkinson's disease dementia ($n = 3$)	Behavioral variant of frontotemporal dementia ($n = 2$)	Vascular dementia ($n = 5$)
1. Requirement of hospitalization	71.4%	75.0%	100%	50.0%	60.0%
Mean duration of stay among hospitalized patients (days)	11.7 ± 7.01	6.7 ± 2.89	18.0 ± 6.25	8.0 ± 0.0	11.7 ± 8.33
2. Requirement of mechanical ventilation	21.4%	0.0%	66.7%	0.0%	20.0%
3. Requirement of high-flow oxygen	50.0%	25.0%	100%	50.0%	40.0%
4. Occurrence of cytokine storm	42.9%	25.0%	100%	0.0%	40.0%
5. Occurrence of stroke	0.0%	0.0%	0.0%	0.0%	0.0%

Table 3
Cognitive profile and neuroimaging features before and following COVID-19

				Pre-COVID-19 (n=14)	Post-COVID-19 (n=14)	p-value
1. Presence of fatigue				14.3 %	92.9 %	0.001
2. Presence of depression				42.9 %	92.9 %	0.016
3. mean FAB score				13.3 ± 2.61	11.9 ± 2.24	< 0.001
4. mean ACE score				68.6 ± 6.4	54.5 ± 7.09	0.001
5. mean Clinical dementia rating score				6.7 ± 1.66	11.9 ± 3.01	0.002
6. Domain - specific score in ACE	(a) Attention			11.3 ± 2.16	7.1 ± 0.95	0.019
	(b) Memory			17.5 ± 3.18	14.6 ± 3.39	< 0.001
	(c) Fluency			9.8 ± 1.22	7.1 ± 1.23	0.006
	(d) Language			18.9 ± 3.51	15.7 ± 4.02	< 0.001
	(e) Visuospatial			11.2 ± 2.19	9.9 ± 2.2	< 0.001
7. Executive function	(a) Clock - drawing test	(i) Normal		35.7 %	7.1 %	0.021
		(ii) Abnormal	Executive	14.3 %	28.6 %	
			Visuospatial	28.6 %	0 %	
			Executive & visuospatial	7.1 %	14.3 %	
			Planning	14.3 %	50.0 %	
	(b) Trail B making	(i) Unable		28.6 %	78.6 %	0.016
		(ii) Able	In less than 2 minutes	42.9 %	0 %	
			In more than 2 minutes	28.6 %	21.4 %	
8. Neuroimaging features	(a) Fazekas periventricular white matter hyperintensities		Grade 0	28.6 %	7.1 %	0.002
			Grade 1	42.9 %	7.1 %	
			Grade 2	28.6 %	71.4 %	
			Grade 3	0 %	14.3 %	
	(b) Fazekas deep white matter hyperintensities		Grade 0	85.7 %	0 %	0.001
			Grade 1	14.3 %	42.9 %	
			Grade 2	0 %	57.1 %	
			Grade 3	0 %	0 %	
	(c) Global cortical atrophy		0	50.0 %	28.6 %	0.025
			1	28.6 %	42.9 %	
			2	21.4 %	21.4 %	
			3	0 %	7.1 %	

been conjectured as a relatively new symptom in dementia [53, 54]. The striking presence of post-COVID-19 fatigue [21, 55–59] might indicate either shared pathomechanisms or similar lesion locations between MS and COVID-19 (Fig. 1A). The pattern of decreased attention, executive dysfunctions, delayed information procession speed, mood changes, and memory impairment retrieved with cues commonly seen in vascular dementia [60–62], which is almost similar to post-COVID-19 cognitive impairment [1–16, 63]. A similar pattern of cognitive impairments is also seen in MS patients [64–71]. Notably, cerebral lesions in MS [72–76], vascular dementia [77–80], and post-COVID-19 [5, 36, 37, 81–84] predominantly and characteristically disrupt the same frontal sub-cortical circuits. Henceforth, it might be held accountable for similar kinds of cognitive impairment.

Similarly, we observed that all patients had white matter hyperintensities on MRI, involving periventricular deep white matter, juxta-cortical white matter, and superficial white matter mimicking lesions seen in MS and small vessel disease leading to vascular dementia [72–84]. Another striking observation has been the presence of fatigue and depression. Depression is very common in dementia and may precede, coincide or follow cognitive symptoms in all types of dementia, especially in Alzheimer's disease and vascular dementia [85–89]. Depression is one important associate of post-COVID-19 cognitive impairment [10, 21, 90]. Disruption of frontal subcortical circuitry or involvement of the cortico-striato-thalamo-cortical loop is thought to be intricately twinning [91–94]. However, environmental factors like loss, loneliness, financial burden, and uncertainty are key players in depression and have been found across different studies [4, 17, 95, 96].

Fatigue is multifactorial. Muscle disease and organ failures are commonly considered in evaluating patients with fatigue. In the post-COVID-19 situation, the pathobiological conundrum has been extended, and the hypothalamic-pituitary-adrenal axis will draw attention in this regard [97–99]. Many studies hold responsible the indiscriminate steroid use during COVID-19 time [100] and modulation of the hypothalamic-pituitary-adrenal axis [101].

Both pathobiological and lesion location-wise, the brain model of MS has numerous similarities with the "post-COVID-19 brain" in terms of inflammation and immune dysregulation triggered by genetic susceptibility and infection, leading to white matter changes, subcortical cognitive impairments, fatigue, and neurodegeneration [102–113]. Researchers may argue against this, as vascular dementia also has similar lesion locations involving white matter tracts; however, patients with vascular dementia usually do not have unusual fatigue. The author's view in this regard is that it is not only the white matter burden, which is responsible for fatigue, but the pathobiological process underneath that has an important role to play. Thus, inflammation in the brain and resultant white matter abnormalities and subsequent neurodegeneration have intriguing relationships underpinning fatigue that authors have proposed, which needs further translational research and substantiation. The presence of cognitive fatigue in all of our patients (which was not present before they suffered from COVID-19), irrespective of the types of dementia, further strengthened the hypothesis proposed.

Post-COVID-19 dementia research will be challenging based on the evidence in this study. There will be more chance of getting a mixed cognitive pattern in the evaluation. In our small but detailed study, all these patients with dementia (irrespective of their types) had obvious addition to pre-existing T2-weighted imaging and T2-FLAIR-weighted intensity changes, and involvement of cognitive domains changed with an added burden of frontal subcortical cognitive impairment, giving them a difficult-to-evaluate mixed picture of dementia. More importantly, it has also been observed that the so-called relatively slowly progressive course of Alzheimer's disease and fluctuations in vascular dementia changed, and a rapid and relentlessly progressive nature emerged. White matter intensity changes (i.e., T2/T2-FLAIR burden) were seen in all patients, albeit a small number of patients in our cohort, had pre-existing conventional vascular risk factors. This has left ample room to consider factors responsible for increasing the white matter burden. Different studies have established multifactorial causation for white matter burden and intensity changes. Direct viral invasion, immune dysregulation, persistent inflammation, and coagulopathies have been considered, proposed, and studied previously without any definitive conclusion [104–111].

Interestingly, we saw that rapid progression of dementia, the addition of further impairments/deterioration of cognitive abilities (mostly subcortical type), and increase or new appearance of white matter lesion burden were common in our patients, irrespective of dementia type, the severity of COVID-19, presence of vascular risk factors, oxygen or ventilator support. This probably inculcates

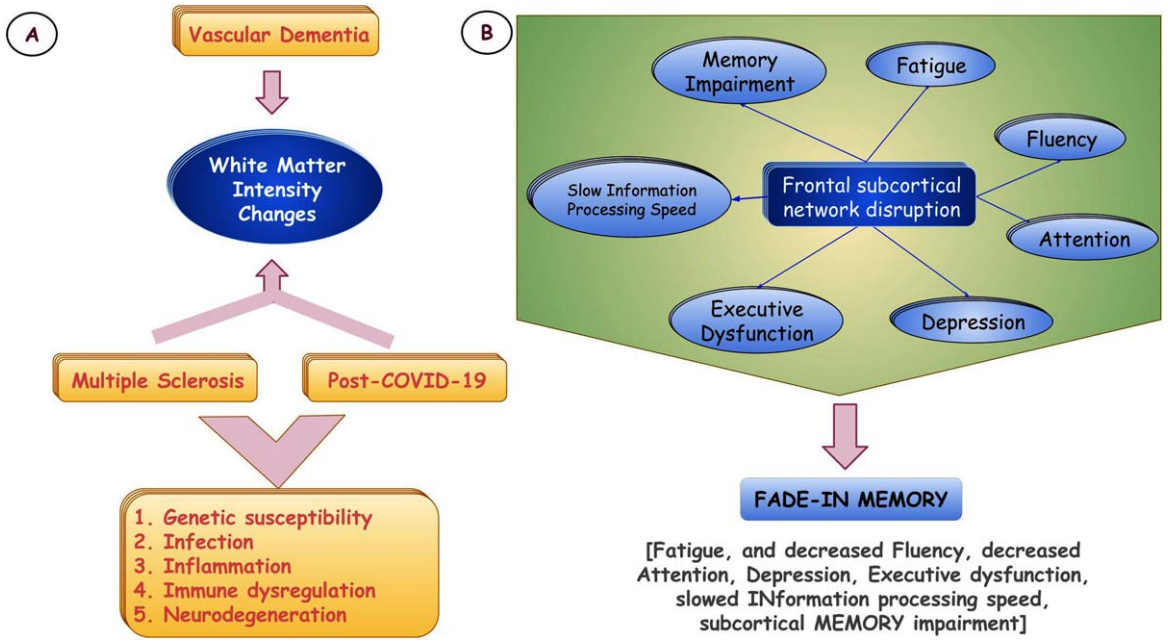

Fig. 1. The possible common pathomechanisms linking multiple sclerosis and post-COVID-19 brain involvement (A). Proposal of a new codename regarding post-COVID-19 cognitive sequelae (B).

the notion that previously compromised brains have little defense to withstand a new insult (i.e., 'second hit' like infection/dysregulated immune response and inflammation), which usually heralds severe cognitive consequences. Moreover, depression, loneliness, uncertainty, loss, fear, and other psychological perspectives on the surge during the COVID-19 pandemic need further attention and be studied to assess their impact on cognitive abilities and white matter tract.

Proposal

'Brain fog' is an ambiguous terminology without specific attribution to the spectrum of post-COVID-19 cognitive sequelae. Based on the progression of cognitive deficits and the association with white-matter intensity changes, we propose a new codename, i.e. 'FADE-IN MEMORY' (i.e., Fatigue, and decreased Fluency, Attention deficit, Depression, Executive dysfunction, slowed INformation processing speed, and subcortical MEMORY impairment) (Fig. 1B). The authors presume it would be more appropriate, befitting, and scientifically apropos with specific attribution of domains involved and associated neuroimaging changes.

The intricate and complex interplay of infection (trigger), immune dysregulation and persistent inflammation, coagulopathies to microangiopathy, demyelination, axonal dropouts, and finally, neurodegeneration leading to predominant subcortical type cognitive impairment, including fatigue and depression, suggests there must have some common pathomechanisms between MS and post-COVID-19 brain involvement (Fig. 1A).

Finally, yet importantly, the authors also put "fatigue" as the single most important 'cognitive biomarker' in their proposal. This cognitive biomarker, i.e. cognitive fatigue, might fill the gaps in our understanding of the post-COVID-19 brain and might be a potential missing dovetail (along with depression and subcortical type of memory impairment) splicing "multiple sclerosis-brain" and "post-COVID-19-brain".

ACKNOWLEDGMENTS

The authors have no acknowledgements to report.

FUNDING

J. Benito-León is supported by the National Institutes of Health, Bethesda, MD, USA (NINDS #R01 NS39422), the European Commission (grant ICT-2011-287739, NeuroTREMOR), the Ministry of Economy and Competitiveness (grant RTC-

2015-3967-1, NetMD—platform for the tracking of movement disorder), and the Spanish Health Research Agency (grant FIS PI12/01602 and grant FIS PI16/00451).

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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