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Neuropsychological Measures of Long COVID-19 Fog in Older Subjects

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KEYWORDS

• Long COVID • Elderly • Cognitive impairment

KEY POINTS

- We asked whether coronavirus disease 2019 can have a long-term impact on cognitive function in the elderly.
- In this cohort study of 100 elderly individuals assessed on average 3 months after acute coronavirus disease 2019, we found a high prevalence of failed neuropsychological tests.
- We found that coronavirus disease 2019 is capable of eliciting persistent measurable neurocognitive alterations in the elderly, particularly in the areas of attention and working memory.

INTRODUCTION

Since December 2019, when the first cases of the coronavirus disease 2019 (COVID-19) were confirmed in the Chinese Hubei region, the pandemic of severe acute

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respiratory syndrome coronavirus 2 continues to plague populations and health systems around the world. A number of descriptions now cover the long-term symptoms of the disease, which include fatigue, shortness of breath, and pain.[1,2] Neurologic involvement and psychological symptoms owing to or related to the disease are described to affect up to one-third of infected people.[3–5] These symptoms include a wide spectrum of manifestations that are often loosely described as a general mental slowness often named foggy brain or COVID fog.[6] Such symptoms can characterize both the acute phase and the convalescent period, during which patients report an ill-defined sense of not feeling their best or of not having fully recovered their previous well-being in the physical, occupational, or social domains.[7] In some studies, cognitive problems were tied to a diagnosis of dementia[5] and concern is particularly high for the aged populations.

Because the availability of clinical data remains poor, the aim of the present study was to investigate the neurologic and cognitive features of a sample of elderly patients with confirmed diagnosis of COVID-19 evaluated in the postacute phase through a direct neuropsychological evaluation.

METHODS

Since April 21, 2020, a postacute outpatient service for individuals recovering from COVID-19 was established at our institution. All patients with a previous diagnosis of COVID-19 who met criteria for discontinuation of quarantine were considered eligible (no fever for 3 consecutive days, improvement in other symptoms, and 2 negative test results for severe acute respiratory syndrome coronavirus 2 taken 24 hours apart).

Once enrolled, each participant underwent a number of evaluations (described elsewere[8]), including a detailed history, neurologic objective examination, and specific anamnesis for general and neurologic symptomatology. For the purpose of this study, we enrolled individuals over the age of 65 years.

Cognitive Evaluation

After the anamnestic evaluation and neurologic objectivity, each patient underwent a neuropsychological evaluation that included Mini Mental State Examination[9] and 8 more specific neuropsychological tests: the Rey Auditory Verbal Test was used to investigate immediate and deferred memory[10]; selective attention and visual–spatial exploration were assessed with Multiple Features Target Cancellation Test[11,12]; the Trial Making Test assessed selective, divided, and alternating, attention together with other features such as psychomotor speed, visuospatial research ability and working memory[13,14]; the Digit Span Forward and Backward evaluated the verbal short-term and working memory capacity[15]; and the Frontal Assessment Battery evaluates composite multidimensional domains and was used to screen for global executive dysfunction including behavioral, affective, motivational and cognitive components.[16,17]

Of each neuropsychological test were reported the raw scores, the scores adjusted for age and educational level and gender (where appropriate), and standardized scores on a 5-point ordinal scale (Equivalent Scores).[18] A test Equivalent Score of 0 was considered pathologic, a score of 1 was classified as borderline, and scores of 2 to 5 were considered consistent with normal performance.

Other Evaluations

Psychiatric domains were evaluated with the Hamilton Anxiety[19,20] and Depression[21,22] scales and the Kessler Psychological Distress scales,[23,24] and anxiety, depressive symptoms, and global psychological distress were evaluated with a cut-off of 7, 7, and 19 in each scale total score, respectively. The Pittsburg Sleep Quality Index[25] was used to assess sleep quality and disturbances.

Case severity was assessed with the 7-category ordinal scale,[26] which classifies participants based on the need for hospitalization and O_2 administration into 1 to 2, nonhospitalized; 3, hospitalized, not requiring supplemental oxygen; 4, hospitalized, requiring supplemental oxygen; 5, hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; 6, hospitalized, requiring invasive mechanical ventilation, extracorporeal membrane oxygenation, or both; and 7, death. Given the differences in the clinical manifestations and severity between sexes,[27] results were also compared by sex.

Statistical Analysis

Descriptive analyses and comparisons were obtained through ANOVA and χ^2 tests where appropriate. The *P* value was set to less than .05 for statistical significance. Given the descriptive basis of the analyses no correction of significance levels was used. All analyses were conducted using R version 4.1.3 (R Foundation, Vienna, Austria).

This study was approved by the Università Cattolica and Fondazione Policlinico Gemelli IRCCS Institutional Ethics Committee. Written informed consent was obtained from all participants.

RESULTS

We present data from 100 individuals (mean age, 73.4 ± 6.1 years; 35% female) assessed at our institution from April 23, 2020, to November 30, 2020. The general characteristics of the study participants, stratified by sex, are described in **Table 1**. Females presented a lower prevalence of diabetes mellitus and a higher prevalence of thyroid disorders. In contrast, males showed less persistence of post–COVID-19 symptoms and on average a smaller decrease in quality-of-life scores.

On average, the assessment was performed 96.5 days after the onset of COVID-19 symptoms. Fatigue was reported by half of the enrolled participants; apart from that, as shown in **Fig. 1**, very high rates of persistent neurologic symptoms were reported in the domains of memory, attention, and sleep. The outcome of neuropsychological testing is described in **Table 2** and **Fig. 2**. On average, the adjusted Mini Mental State Exam score was 28.2 ± 1.7, as expected in a study sample consisting of fairly educated individuals with no history of cognitive impairment. No significant differences were observed within the severity groups. Importantly, 33%, 23%, and 20% of participants achieved either pathologic or borderline performances on the Trial Making, Digit Span Backwards, and Frontal Evaluation Battery tests, respectively. It is also notable that on the neuropsychological assessment a total of 33 participants were found to perform at a level considered to be pathologic.

DISCUSSION

This single-center study investigated the cognitive status of a group of elderly people post–COVID-19 through a battery of neuropsychological tests. Interviewed on average 3 months after the onset of the first symptoms of COVID-19, a significant

Table 1
Sample characteristics

	Total	Males	Females	*p*
	n = 100	n = 65	n = 35	
General information				
Age (years)	73.4 (6.1)	73.4 (5.8)	73.5 (6.7)	0.957
Females	35 (35%)			
BMI (kg/m^2)	26.1 (3.9)	26.2 (3.7)	25.9 (4.1)	0.695
Education (years)	12.7 (8.7)	13.0 (5.5)	12.2 (12.7)	0.678
Not employed	80 (80%)	51 (78.5%)	29 (82.9%)	0.793
Flu vaccination	53 (53%)	40 (61.5%)	13 (37.1%)	0.046
Antipneumococcal vaccination	21 (21%)	17 (26.2%)	4 (11.4%)	0.16
Regular physical activity	60 (60%)	37 (56.9%)	23 (65.7%)	0.784
Smoking status				0.115
Nonsmoker	37 (37%)	20 (30.8%)	17 (48.6%)	
Active smoker	6 (6%)	5 (7.7%)	1 (2.9%)	
Former smoker	52 (52%)	38 (58.5%)	14 (40%)	
Unknown	5 (5%)	2 (3.1%)	3 (8.6%)	
Pre-COVID clinical features				
Cardiovascular conditions	69 (69%)	49 (75.4%)	20 (57.1%)	0.098
Chronic heart disease	19 (19%)	16 (24.6%)	3 (8.6%)	0.092
Atrial fibrillation	12 (12%)	7 (10.8%)	5 (14.3%)	0.847
Heart failure	8 (8%)	6 (9.2%)	2 (5.7%)	0.817
Stroke	2 (2%)	0 (0%)	2 (5.7%)	0.231
Hypertension	58 (58%)	41 (63.1%)	17 (48.6%)	0.234
Diabetes mellitus	19 (19%)	17 (26.2%)	2 (5.7%)	0.027
Renal failure	9 (9%)	6 (9.2%)	3 (8.6%)	1
Thyroid disease	24 (24%)	9 (13.8%)	15 (42.9%)	0.003
COPD	22 (22%)	15 (23.1%)	7 (20%)	0.919
Active cancer	7 (7%)	4 (6.2%)	3 (8.6%)	0.967
Immune disease	8 (8%)	3 (4.6%)	5 (14.3%)	0.189
COVID-19 events				
Seven category ordinal scale				0.092
2. Not hospitalized	12 (12%)	5 (7.7%)	7 (20%)	
3. Hospitalized, not requiring O_2	14 (14%)	6 (9.2%)	8 (22.9%)	
4. Hospitalized, requiring O_2	43 (43%)	31 (47.7%)	12 (34.3%)	
5. Hospitalized, requiring HFNC/NIV	16 (16%)	12 (18.5%)	4 (11.4%)	
6. Hospitalized, requiring intubation/ECMO	15 (15%)	11 (16.9%)	4 (11.4%)	
Drug treatments				
Treatment for COVID-19 pneumonia	81 (81%)	56 (86.2%)	25 (71.4%)	0.128
Anti retrovirals	80 (80%)	56 (86.2%)	24 (68.6%)	0.067
Hydroxychloroquine	80 (80%)	55 (84.6%)	25 (71.4%)	0.19
Anti-IL6	40 (40%)	29 (44.6%)	11 (31.4%)	0.29
Azithromycin	42 (42%)	31 (47.7%)	11 (31.4%)	0.174
Other antibiotics	48 (48%)	35 (53.8%)	13 (37.1%)	0.166

(*continued on next page*)

Table 1
(*continued*)

	Total	Males	Females	*p*
	n = 100	n = 65	n = 35	
Enoxaparin	73 (73%)	47 (72.3%)	26 (74.3%)	1
Corticosteroids	15 (15%)	9 (13.8%)	6 (17.1%)	0.883
Antiplatelet drugs	19 (19%)	16 (24.6%)	3 (8.6%)	0.092
Length of stay (days)	23.3 (16.1)	25.4 (15.8)	18.8 (16.0)	0.072
Post COVID-19				
Days since first symptoms	96.5 (45.3)	93.2 (40.7)	102.7 (52.8)	0.319
Days since hospital discharge	62.1 (39.7)	58.3 (34.4)	70.2 (48.9)	0.25
N. persistent symptoms	3.0 (2.5)	2.6 (2.3)	3.8 (2.9)	0.02
Persistent symptoms				0.114
No symptoms	17 (17%)	14 (21.5%)	3 (8.6%)	
1–2 symptoms	33 (33%)	23 (35.4%)	10 (28.6%)	
≥3 symptoms	50 (50%)	28 (43.1%)	22 (62.9%)	
Decrease in QoL (EQ-VAS)	−10.1 (14.0)	−7.7 (13.1)	−14.7 (14.8)	0.022

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; EQ-VAS, EuroQol visual analog scale; HFNC, high-flow nasal cannulae; NIV, noninvasive ventilation; QoL, quality of life.

proportion of participants reported persistent sleep (33%), attention (30%), and memory (30%) symptoms. These findings are consistent with several previous studies[5,28] and the well-established notion that COVID-19 leaves behind a burden of persistent symptoms pertaining to many organ systems.[1]

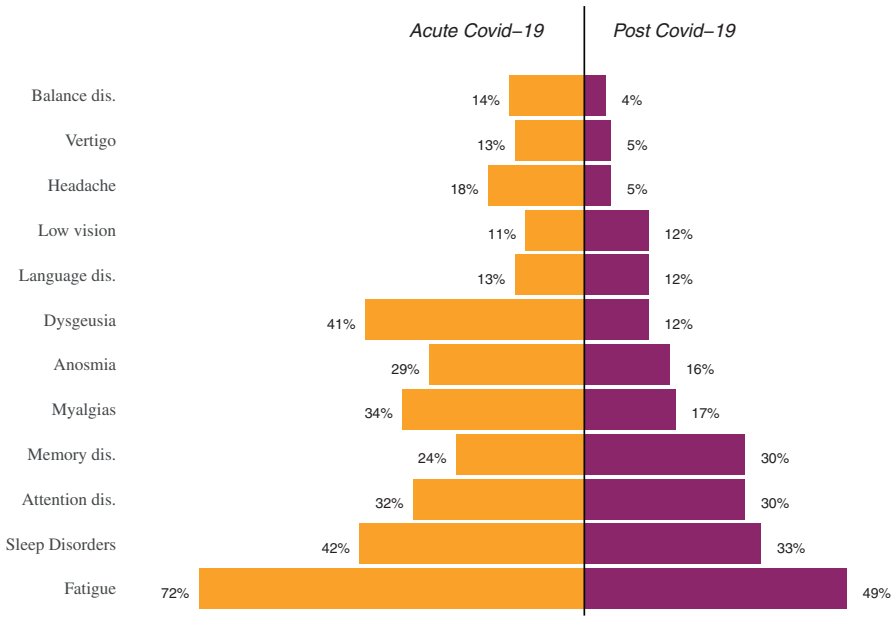

Fig. 1. Neurologic symptoms reported in the acute and recovery phase.

Table 2
Neuropsychological tests

		Sex			Severity – Seven Category Ordinal Scale					
					Not Hospitalized	Hospitalized				
	Total	Males	Females	*P* Value	2. At Home	3. No O_2	4. O_2	5. HFNC/ NIV	6. Intubation/ ECMO	*P* Value
	n = 100	n = 65	n = 35		n = 12	n = 14	n = 43	n = 16	n = 15	
MMSE										
Corrected	28.2 (1.7)	28.4 (1.7)	27.7 (1.8)	0.068	28.2 (1.9)	28.5 (1.5)	27.9 (2.1)	28.2 (1.3)	28.7 (0.8)	0.48
Rey's immediate recall										
Corrected	42.6 (7.8)	41.8 (8.0)	44.1 (7.3)	0.171	43.1 (7.0)	42.5 (8.7)	41.7 (7.5)	42.8 (8.8)	44.7 (8.0)	0.804
Equivalent	3.1 (1.1)	3.0 (1.2)	3.5 (0.9)	0.044	3.4 (0.9)	3.1 (1.1)	3.0 (1.2)	3.1 (1.1)	3.5 (1.1)	0.638
Failed	2 (2%)	2 (3.1%)	0 (0%)		0 (0%)	0 (0%)	1 (2.3%)	0 (0%)	1 (6.7%)	
Borderline	9 (9%)	8 (12.3%)	1 (2.9%)		0 (0%)	2 (14.3%)	5 (11.6%)	2 (12.5%)	0 (0%)	
Rey's delayed recall										
Corrected	8.7 (2.9)	8.2 (2.9)	9.5 (2.7)	0.03	9.5 (2.7)	9.0 (2.8)	8.1 (2.9)	8.4 (3.1)	9.6 (2.8)	0.327
Equivalen	3.0 (1.3)	2.8 (1.3)	3.3 (1.2)	0.03	3.3 (1.2)	3.0 (1.5)	2.8 (1.3)	2.7 (1.4)	3.3 (1.2)	0.58
Failed	7 (7%)	6 (9.2%)	1 (2.9%)		0 (0%)	1 (7.1%)	4 (9.3%)	1 (6.2%)	1 (6.7%)	
Borderline	10 (10%)	6 (9.2%)	4 (11.4%)		2 (16.7%)	2 (14.3%)	3 (7%)	3 (18.8%)	0 (0%)	
MFTC										
Time corrected	50.8 (31.7)	51.4 (25.5)	49.7 (41.3)	0.797	44.4 (26.7)	58.4 (26.1)	48.6 (36.4)	46.9 (25.4)	59.3 (32.5)	0.522
Time equivalent	3.8 (0.8)	3.8 (0.6)	3.6 (1.0)	0.133	3.6 (1.0)	3.6 (0.9)	3.8 (0.7)	3.9 (0.3)	3.7 (1.0)	0.703
Failed	2 (2%)	1 (1.5%)	1 (2.9%)		0 (0%)	0 (0%)	1 (2.3%)	0 (0%)	1 (6.7%)	
Borderline	2 (2%)	0 (0%)	2 (5.7%)		1 (8.3%)	1 (7.1%)	0 (0%)	0 (0%)	0 (0%)	
False alarms corrected	0.7 (2.5)	0.6 (2.9)	0.7 (1.3)	0.858	2.6 (6.4)	0.8 (1.9)	0.4 (1.0)	0.2 (0.8)	0.3 (0.8)	0.651
False alarms equivalent	3.5 (1.1)	3.7 (0.9)	3.2 (1.4)	0.042	2.8 (1.8)	3.4 (1.2)	3.6 (0.9)	3.7 (1.0)	3.7 (1.0)	0.149

Failed	7 (7%)	3 (4.6%)	4 (11.4%)		3 (25%)	1 (7.1%)	1 (2.3%)	1 (6.2%)	1 (6.7%)	
Borderline	2 (2%)	1 (1.5%)	1 (2.9%)		0 (0%)	0 (0%)	2 (4.7%)	0 (0%)	0 (0%)	
Frontal Assessment Battery										
Corrected	15.8 (1.9)	15.9 (1.8)	15.7 (2.1)	0.717	16.1 (2.2)	15.6 (2.0)	15.9 (1.9)	15.9 (1.1)	15.6 (2.2)	0.952
Equivalent	2.8 (1.4)	2.9 (1.4)	2.7 (1.5)	0.556	2.8 (1.6)	2.8 (1.4)	2.8 (1.4)	2.9 (1.1)	2.6 (1.8)	0.978
Failed	12 (12%)	6 (9.2%)	6 (17.1%)		2 (16.7%)	2 (14.3%)	4 (9.3%)	0 (0%)	4 (26.7%)	
Borderline	8 (8%)	7 (10.8%)	1 (2.9%)		1 (8.3%)	0 (0%)	5 (11.6%)	2 (12.5%)	0 (0%)	
Digit Span Forward										
Corrected	6.0 (1.1)	6.0 (1.1)	5.9 (1.1)	0.444	5.8 (0.9)	5.8 (1.1)	6.0 (1.1)	6.2 (1.2)	6.0 (1.0)	0.918
Equivalent	3.2 (1.3)	3.2 (1.2)	3.1 (1.4)	0.479	3.2 (1.3)	2.9 (1.6)	3.2 (1.3)	3.4 (1.3)	3.1 (1.1)	0.917
Failed	8 (8%)	4 (6.2%)	4 (11.4%)		1 (8.3%)	2 (14.3%)	4 (9.3%)	1 (6.2%)	0 (0%)	
Borderline	4 (4%)	3 (4.6%)	1 (2.9%)		0 (0%)	1 (7.1%)	1 (2.3%)	1 (6.2%)	1 (6.7%)	
Digit Span Backwards										
Corrected	4.1 (1.0)	4.2 (1.0)	3.9 (1.0)	0.26	4.3 (0.8)	4.0 (0.8)	4.1 (1.0)	3.8 (0.9)	4.1 (1.1)	0.701
Equivalent	2.7 (1.3)	2.8 (1.3)	2.5 (1.4)	0.279	3.1 (1.2)	2.6 (1.2)	2.8 (1.4)	2.6 (1.5)	2.6 (1.4)	0.852
Failed	8 (8%)	4 (6.2%)	4 (11.4%)		0 (0%)	0 (0%)	5 (11.6%)	2 (12.5%)	1 (6.7%)	
Borderline	15 (15%)	8 (12.3%)	7 (20%)		2 (16.7%)	3 (21.4%)	4 (9.3%)	3 (18.8%)	3 (20%)	
Trail Making										
Corrected	118.2 (100.6)	93.9 (86.8)	163.5 (109.7)	<.001	185.2 (121.7)	94.3 (91.1)	112.2 (99.2)	98.4 (89.8)	125.5 (94.8)	0.136
Equivalent	2.3 (1.5)	2.7 (1.4)	1.6 (1.5)	<.001	1.5 (1.7)	2.9 (1.5)	2.4 (1.6)	2.4 (1.4)	2.1 (1.4)	0.231
Failed	21 (21%)	8 (12.3%)	13 (37.1%)		6 (50%)	2 (14.3%)	8 (18.6%)	2 (12.5%)	3 (20%)	
Borderline	11 (11%)	7 (10.8%)	4 (11.4%)		0 (0%)	0 (0%)	6 (14%)	3 (18.8%)	2 (13.3%)	

Abbreviations: ECMO, extracorporeal membrane oxygenation; HFNC, high-flow nasal cannulae; MFTC, Multiple Features Target Cancellation test; MMSE, Mini Mental State Exam.

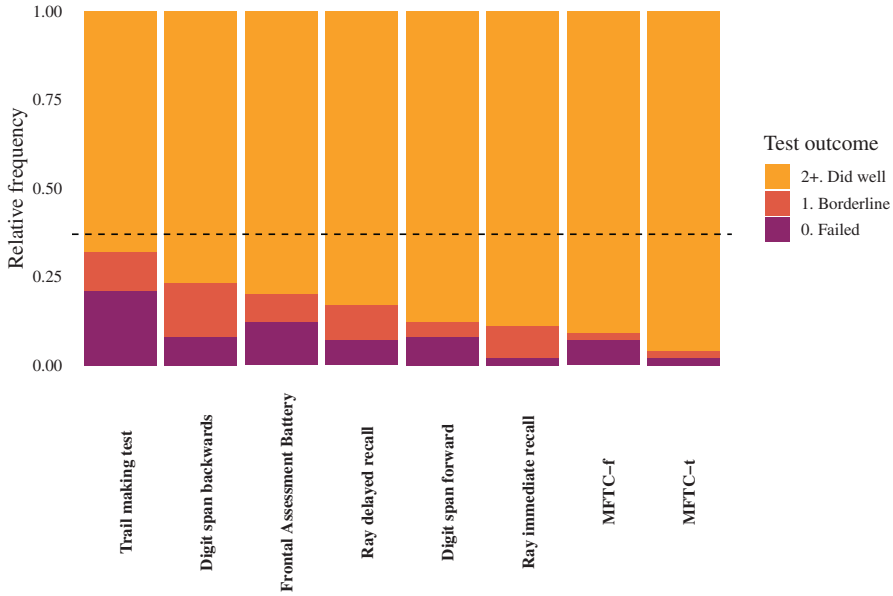

Fig. 2. Neuropsychological tests. The figure shows, for each neuropsychological test, the proportion of patients with fair (*light color*), borderline (*darker color*) or failed (*dark color*) outcome. Equivalent scores (ES) were used to rate participants: those with a score of 2 or more, 1, or zero were classified as having normal, borderline or pathologic performance respectively. Horizontal dashed line indicates the overall prevalence of participants classified as having a pathologic neuropsychological test (ie, $\geq$1 ES of zero and $\geq$1 ES of 1) MFTC, Multiple Features Target Cancellation test.

When directly tested with the neuropsychological battery, 33%, 23%, and 20% of participants failed the Trial Making, Digit Span Backwards, and Frontal Evaluation Battery tests, respectively, showing impairment in visuoperceptual skills, selective and divided attention, working memory, short-term verbal memory, and executive functions. These data expand the preliminary knowledge acquired in 2 previous studies with evidence of attention deficit,[29] visuoperception, naming, and fluency.[30]

An important finding from the study is that approximately 1 in 3 participants presented at neuropsychological tests with at least 1 overtly pathologic score in conjunction with at least 1 borderline pathologic test. This finding, together with average Mini Mental State Exam scores above the cutoff of 23 could represent a rough estimate of post–COVID-19 mild cognitive impairment. Such a value does not differ from that obtained in other studies based on telephone interviews.[31]

This study had many methodological limitations owing to the design and circumstances under which it was conducted. It is a single-center study with no control group or longitudinal follow-up. In addition, after an initial phase in which people were contacted from the hospital's patient lists, later people from the local area began to request to be followed at our center. Therefore, it is not possible to exclude that people with a greater burden of disease were included. Importantly no premorbid neuropsychological evaluation was available. Indeed, the sole use of neuropsychological tests could have inaccurately estimated the problem because an unknown proportion of participants could have presented pathologic performance on tests, regardless of COVID-19.

SUMMARY

COVID-19 is capable of eliciting persistent neurocognitive alterations. These alterations are measurable with widely available test batteries and seem particularly relevant in the areas of executive functions in general and attention and working memory specifically. In the context of this ongoing pandemic, it is imperative to intensify and expand research in the field as these cognitive derangements may represent an early stage of mild cognitive impairment in the elderly.

CLINICS CARE POINTS

- For many elderly people, Covid-19 represents an event with non-negligible cognitive sequelae.
- Since in many cases these people have never been previously studied cognitively, the clinician is confronted with the question of whether what is being observed is a more or less temporary effect of Covid-19 or on the contrary represents the onset of a cognitive impairment of a different nature although possibly triggered or made more readily apparent by Covid-19.
- In this sensitive population group, therefore, we recommend to proactively look for emerging cognitive deficits and to plan a reassessment of the cognitive picture at regular intervals.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.cger.2022.05.003.

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