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Neurologic and cognitive sequelae after SARS-CoV2 infection: Different impairment for ICU patients

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ABSTRACT

The exact incidence of neurological and cognitive sequelae of COVID-19 in the long term is yet unknown. The aim of this research is to investigate the type of neurological and cognitive impairment in COVID-19 cases of different severity. Two hundred fifteen patients, who had developed COVID-19, were examined 4 months after the diagnosis by means of neurological exam and extensive cognitive evaluation, investigating general cognition, memory, verbal fluency, visuospatial abilities and executive functions. Fifty-two of them were treated in intensive care unit (ICU patients), whereas 163 were not hospitalized (non-ICU patients). Neurological deficits were found in 2/163 (1.2%) of non-ICU and in 7/52 (13.5%) of the ICU cases, all involving the peripheral nervous system. ICU patients performed significantly worse in all the neuropsychological tests and showed a worse age- and education-corrected cognitive impairment: Cognitive Impairment Index (CII) was higher in ICU than in non-ICU patients (median ICU 3 vs 2, $p = .001$). CII significantly correlated with age in both groups, was unrelated to length of follow- up, diabetes and hypertension and - only for ICU patients- to PaO_2/FiO_2 at ICU admission. Obtained results support the greater susceptibility of COVID-19 patients, treated in ICU, to develop neurological deficits and cognitive impairment at a four-month follow up, as compared to cases with mild/moderate symptoms.

1. Introduction

Long COVID has gained prominence in recent months, as many patients report, months after the acute SARS CoV2 infection, both general symptoms, such as dyspnea and fatigue [1], specific neurological symptoms, such as hyposmia, hypogeusia and neurological diseases including headache, paresis of limbs, Guillain Barrè syndrome [2]. Several patients also report subjective "brain fog" and emotional disorders, such as anxiety or depression, leading to reduced activity or need for psychological support or psychiatric interventions [3]. For example, Morin et al. [4] recently reported that 244 COVID-19 patients (51% of the whole sample) declared at least 1 symptom that did not exist before, when assessed at four months after the acute infection: fatigue in 31%, cognitive symptoms in 21%, and dyspnea in 16%. Cognitive impairment, directly assessed on a subgroup of these patients (defined as below average scores in MoCA or d2-R tests), was detected in 38% of the examined patients.

Other series have also shown that some patients develop persistent and debilitating neuropsychiatric symptoms, despite a relatively mild COVID-19 and young age [5]. These patients are named as "long

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haulers" [6,7]. The pathogenesis of these disturbances remains unclear; the possible direct viral invasion of the CNS seems unlikely and some similarities with chronic fatigue syndrome and fibromyalgia have been suggested [8].

The real incidence of long term cognitive impairment related to COVID-19 is limited by several factors, i.e. the self-selection of patients seeking help at the COVID clinics, the use – in the majority of published papers- of self-reported measures to investigate cognitive deficits, instead of formal neuropsychological evaluations. These factors may lead to misinterpretations about the real nature of symptoms reported and about the exact incidence of cognitive deficits. Thus, multiple initiatives were recently launched worldwide [9], to gather clinical neurological data about COVID-19, with the aim to aid management and to understand the long-term clinical manifestations of the disease.

We have recently reported [10] no evidence of measurable cognitive impairment in a cohort of healthcare workers (HCW) in Brescia, Italy, previously infected by SARS-CoV-2 and undergoing an extensive neuropsychological test battery covering most cognitive functions four months after the disease. On the other hand, these patients showed significantly greater anxiety, depression and stress scores on psychological questionnaires, suggesting an emotional rather than cognitive disturbance as a main consequence of COVID-19. Although the disease severity of this sample was mild to moderate and only two patients needed tracheal intubation and intensive care unit (ICU) admission, this study had a control group of healthy cases and focused on a well-defined sample group.

It has been recently reported that neurological manifestations of acute COVID-19 are prevalent among hospitalized patients and are associated with higher in-hospital mortality [11] whereas no data are available on the association between COVID-19 severity and long-term neurological and cognitive symptoms.

The present study was performed with the main aim of comparing neurological and cognitive functions at four month follow-up in patients suffering mild to moderate COVID-19 vs patients requiring intensive care unit (ICU) admission.

2. Methods

This prospective observational study was conducted at the University Hospital of Brescia, including 215 patients (older than 18 years) who had been previously affected by symptomatic COVID-19 (confirmed diagnosis by means of a positive result on a molecular nasopharyngeal swab). They were enrolled in an observational study, aimed at prospectively evaluating the health status after COVID-19 and were all examined a mean of 4 months after diagnosis. A written informed consent was obtained by each patient and the study followed the Ethics principles of the Helsinky Declaration. The study followed STROBE reporting guidelines. According to the National Institutes of Health guidelines (*https://www.covid19treatmentguidelines.nih.gov/*), the severity of the disease was anamnestically defined as mild, moderate, severe or critical. 163 patients had a mild (various signs and symptoms of COVID-19 without dyspnea or positive chest XRay exam) or moderate (evidence of lower respiratory disease at clinical assessment or imaging, but oxygen saturation $SpO_2 \geq 94\%$) disease and did not require oxygen support (non-ICU patients). 52 had a severe ($SpO_2 < 94\%$ on room air, $PaO_2/FiO_2 < 300$ mmHg, respiratory frequency > 30 breaths/min, or lung infiltrates >50%) or critical (respiratory failure, septic shock, and/or multiple organ dysfunction) illness and required ICU admission (ICU patients).

The follow-up included a targeted clinical diagnostic assessment with neurological exam and a detailed neuropsychological evaluation at the Neuropsychology Unit of the same Hospital. Cranial nerve exam, muscle strength, deep tendon reflexes, sensory and coordination functions were assessed by a board-certified neurologist. To comprehensively analyze all the cognitive functions potentially affected by COVID-19, we chose an extensive neuropsychological tests' battery usually used to investigate patients with brain diseases. We added it to the MMSE, a test of general cognition [12], which is not sufficiently sensitive to show mild and specific changes in cognitive abilities [13]. Verbal and non-verbal memory, visuospatial and executive abilities and verbal fluency by semantic and phonemic cues were separately assessed [14]. All the test results were corrected for age and education, according to published Italian norms, in order to determine if each score resulted within normal values or impaired (less than 2 z scores from the norm). The number of impaired neuropsychological tests was also calculated for each subject. Furthermore, in order to obtain a numerical variable expressing the severity of cognitive impairment, a Cognitive Impairment Index (CII) was computed for each patient [15], by scoring z scores as it follows: if z is 0 to1 a graded score of 0 was given, if z is 0 to -1 a score of 1, if z was -1 to -2 a score of 2 was given, etc. An absolute CII was obtained for each patient by summing these graded scores, expressing the severity of cognitive impairment: since negative z scores indicate a worse performance, higher absolute CII indicates worse cognitive impairment.

The following tests were used: Controlled Oral Word Association by categories and phoneme (COWA-S and COWA-Ph) [16] for word fluency, Rey figure copy and recall [17] for visuospatial abilities and non-verbal memory, immediate and delayed recall of California Verbal Learning Test in non-ICU cases (CVLT) and immediate and delayed recall of Rey Auditory Verbal Learning Test (RAVLT) in ICU cases [18,19]. Notably, percentages of correct responses were used for each memory test for comparing raw scores, whereas age and education corrected z scores were used for each single test when CII was calculated. Tower of London test (TOL) [20] was used for testing the executive abilities. The study followed STROBE guidelines.

The database was formatted through the Microsoft-Excel® software and later imported from the IBM-SPSS® software ver. 26.0.1 (IBM SPSS Inc. Chicago, Illinois). The use of the Stata® software ver. 16.0 (Stata Corporation, College Station, Texas) was also considered for comparisons or implementations of test output. Normality of the distributions was assessed using the Kolmogorov-Smirnov test. Categorical variables were presented as frequencies and percentages and compared with the use of the Chi-Square test or the Fisher's exact test, as appropriate. Continuous variables were presented as means ±SD (in case of a normal distribution), or medians and minimum-maximum range (in case of a skewed distribution) and compared with the use of Student's t-test, ANOVA, or the Mann-Whitney and Kruskal-Wallis test; correlations among variables by the Pearson's or Spearman's rank correlation test.

Analysis of covariance (ANCOVA) and univariate linear regression were also performed to study the relationships among dependent and independent variables. A two-sided α level of 0.05 was used for all tests.

3. Results

Demographic and clinical characteristics of ICU and non-ICU COVID-19 patients are reported in Table 1. ICU patients were older and had lower education level; they were also different by male/female percentages; ICU patients were more frequently affected by diabetes and hypertension but did not differ from non-ICU patients in the prevalence of obesity or pre-existing respiratory diseases. ICU patients were examined at a mean of 141 days (SD 4,22) after COVID-19 diagnosis and non-ICU were examined at a mean of 121 days (SD 41,21) after COVID-19 diagnosis (Student's t-test p: n.s.). All the non-ICU patients, during the acute disease, suffered respiratory symptoms, 10% of them also had had a positive chest X Ray for interstitial pneumonia. Noteworthy, pneumonia may have been underestimated in non-hospitalized patients. Disease duration in non-ICU patients (time from the first positive molecular swab test to the first negative molecular swab was 22 days (median, range 5–72). Among those precisely reporting therapy, only 5% were treated with lopinavir/ritonavir combination, 16.7% with hydroxychloroquine and 5% with steroids. Antibiotics and anti-inflammatory drugs were also present, at various extent, in the medical history of home therapies.

Table 1
Demographic and clinical characteristics of COVID-19 and non-COVID-19 subjects.

	ICU patients	Non-ICU patients	*p*
N	52	163	
Age years mean (SD)	60 (9.9)	46.9 (9.4)	<0.001*
Male /Female number (%)	40 (77)/12 (23)	40(25)/123 (75)	<0.001**
Years of education Median [range]	12 [5–18]	14.9 [8–40]	<0.001*
Comorbidities, N (%)			
Hypertension	27 (52)	29 (17.7)	<0.001**
Diabetes	12 (23)	6 (3.68)	<0.001**
Obesity	8 (15.3)	15 (9.2)	n.s.**
Respiratory diseases	3 (5.7)	6 (3.68)	n.s.**
Respiratory support, N (%)			
O2 therapy	–	163 (100)	
CPAP	8 (15.3)	–	
Mechanical ventilation	43 (82,6)	–	
O2 support	1 (1.9)	–	
Follow up impaired neurological exam N (%)	7 (13.4)	2(1.2)	

.*Mann Whitney *U* test, ** Chi squared test. N.s. (not significant) = $p \geq .05$.

All ICU patients suffered a severe or critical COVID-19 and 43 of them (82%) matched the definition criteria of acute respiratory distress syndrome (ARDS). PaO2/FiO2 at ICU admission was <100 mmHg in 22 cases and >100 (up to 200) mm Hg in 21 patients (data missing for others). Mean length of ICU hospitalization was 15 (range 1–93) days. All ICU patients received oxygen support: 43 received mechanical ventilation (MV), 8 were ventilated with continuous positive airways pressure (CPCP) and 1 received only O2 support with mask. Enoxaparine was regularly used, as well as appropriate antibiotic therapy, tocilizumab was administered in one patient, steroids were used in 16 cases for a mean duration of 5.8 days (dexametazone 20 mg daily e.v. for 10 days followed by 10 mg for other 10 days). Nineteen patients (36%) underwent tracheostomy, 8 (15%) had been pronated at some extent, none needed ECMO. During hospitalization two patients suffered Guillain Barrè syndrome (3%), 7 patients (13%) pulmonary embolism. No patient showed a stroke or encephalitis.

At 4-month follow-up, neurological examination was normal in the vast majority of non-ICU cases: in particular 2 patients (1% of non-ICU) showed limb areflexia and sensory loss with radicular distribution (L5 and S1 respectively) due to preexisting lumbar disc herniation. Seven of the ICU patients had impaired neurological examination (13%): 4 (7%) of them showed reduced tendon reflexes in both legs, 1 (1.9%) had reduced tactile sensation in the thigh, 1 (1.9%) showed new onset essential tremor, 1 (1.9%) showed hyposthenia and areflexia in the left arm, without sensory deficits. A peripheral neuropathy was diagnosed in the first 4 cases, a right femoral-cutaneous neuropathy in 1 case, essential tremor in 1 case, a plexopathy of the lower part of the brachial plexus was diagnosed in 1 case.

MMSE resulted within normal limits in all enrolled patients, with a statistically significant lower score in ICU patients (Table 2). Raw mean scores of all the neuropsychological tests resulted significantly lower in ICU than in non-ICU patients. Median CII was significantly higher in ICU (3; range 0–19) compared to non-ICU patients (2; range 0–16; Mann Whitney $p = .001$), showing a more severe cognitive impairment in ICU patients when controlled for age and education (Table 2). The mean number of impaired tests was higher – though non-significantly- in ICU than in non-ICU (0.61; SD 1.44 and 0.54; SD 1.01 respectively). A significant correlation between age and CII was found in both ICU and in non-ICU patients ($r = 0.37$; $p = .006$ and $r = 0.3$ $p = .000$ for ICU and non-ICU respectively).

The cognitive tests that resulted more frequently impaired in non-ICU patients were: TOL (in 24 cases, 15%), Rey figure recall (in 13 cases, 8%), Rey figure copy (in 8 cases, 5%). Among ICU patients, the corresponding figures were: 10 (19.2%), 5 (9,6%) and 6 (11,5%) cases. In such group, the impairment included also the verbal memory test (delayed RAVLT in 4 cases (7,7%); immediate RAVLT in 3 patients (5,7%).

Table 2
Neuropsychological tests'scores and CII in ICU and non-ICU patients.

	ICU patients	Non-ICU patients	*p**
CII Median [range]	3[0–19]	2[0–16]	0.001
Number of impaired tests Mean [SD]	0.61[1.44]	0.54[1.01]	n.s.
Test's scores Median [range]			
MMSE	29 [26–30]	29 [27–30]	0.01
COWA S	48 [29–70]	46 [19–61]	0.08
COWA Ph	39 [15–59]	37 [3–58]	0.036
OVMT Immediate	55[24–100]	70 [0–95]	0.000
OVMT Delayed	60 [20–100]	86 [0–107]	0.000
TOL	15 [0–22]	16 [1–22]	0.003
Rey figure copy	32 [18–36]	34 [18–36]	0.001
Rey figure recall	14.5 [5–27]	18 [2–31]	0.005

CII: age/education corrected cognitive impairment index; MMSE: Mini Mental State Examination; COWA: Controlled Oral Word Association S: Semantic; Ph: phonemic; OVLT: Oral Verbal Learning Test; TOL: Tower of London.
* Mann Whitney *U* test.

Linear regression showed that in both the study groups the time from disease onset to neurologic evaluation did not significantly influence test's scores and CII; CII was not significantly influenced by the higher frequency of hypertension and diabetes in the ICU group. No significant correlation was observed in ICU patients between CII and pO2/FiO2 at admission.

4. Discussion

In the present study we showed that, at an average four-month follow-up, neurological deficits and cognitive impairment are more frequently observed in severe COVID-19 patients undergoing ICU than in those suffering a mild disease non requiring oxygen support.

In our sample, neurological deficits were due to peripheral nervous system (PNS) involvement, mainly attributable to peripheral neuropathies (Guillain Barrè Syndrome, brachial plexopathy, mononeuropathy), whereas focal signs of central nervous system (CNS) involvement were not present. Importantly, although ICU patients were older an had minor schooling, age and education, corrected CII confirmed a significantly greater cognitive impairment. The characteristics of such cognitive impairment are not similar to those ones typical of degenerative dementia – notably, MMSE was normal-, but are rather characterized by mild deficits in multiple functions, with predominant involvement of executive deficits, as shown by the frequently observed impaired score in TOL, and -to a lesser extent- in memory, as shown by impairments in Rey figure recall and verbal memory tests.

The reasons for such findings are not completely understood. It has been speculated that SARS-CoV-2 may directly access the brain, having a broad organotropism, particularly in kidneys, liver, heart, as shown by autopsies of patients deceased with COVID-19 [21]. However, the virus has not been detected in the cerebrospinal fluid of most of individuals suffering COVID-19 and encephalopathies so far, and a direct viral invasion of the brain has not been clearly demonstrated in neuropathological studies [22,23].

Recently, a reduced cortical metabolism in subacute COVID-19 has been reported [24]. In a group of 29 COVID-19 subacute cases with neurological symptoms and abnormal findings at brain MRI (microembolic subacute infarcts), 18FDG PET scan revealed a predominantly frontoparietal hypometabolism in many patients, related to the severity of cognitive impairment. Notably, a pronounced microglial activation within the white matter, sparing the cortical grey matter, without

irreversible neocortical damage was found in post-mortem brain neuropathology. These data suggest a neocortical dysfunction, at least in subacute COVID-19 hospitalized patients and are interpreted as the result of a prevalent white matter and brainstem pathology rather than a direct cortical damage due to the viral invasion [24]. Our data support the persistence of cognitive impairment in the long term, at least in severe cases of COVID-19 and, in agreement with the Hosp et al. study [24], support the notion of a long lasting prominent deficit in executive and memory functions.

It is possible that a significant proportion of the high burden of neurologic signs and symptoms reported in hospitalized patients with severe COVID-19 are due to critical illness, vascular or metabolic encephalopathy. A severe COVID-19 requiring ICU admission often is associated with a myriad of conditions that may underlie clinical neurologic syndromes and lead to CNS injury. The ARDS caused by COVID-19 and the severe complications such as respiratory or cardiac failure are independently associated with diminished neurologic function in patients who survive these events. The vascular brain damage may possibly be mediated by endothelial injury induced by the virus via ACE2 receptor, or by other mechanisms, typical of more severe clinical conditions, such as those associated with mechanical ventilation requiring prolonged sedation, vasopressor therapy for cardiovascular support, prone positioning, all associated with impairment or injury in diverse components of the neuroaxis [25].

The clinical observation that acute encephalopathy is more frequent in hospitalized COVID-19 compared to other viral infections more typically limited to respiratory dysfunction, may in part be related to the more extensive extra-pulmonary involvement of SARS-CoV2 and particularly to the associated immune responses.

Immune-mediated processes are considered relevant contributors to the pathogenesis of CNS symptoms and syndromes associated with SARS-CoV-2, including cytokine production, T cell activation and other autoimmune activities [26]. A deregulated host immune response in the CNS, caused by compartmentalized activated and expanded lymphocyte and monocyte populations, with both antiviral and anti neural reactivity have been proposed [27]. All these conditions have been reported more frequently in patients with severe or critical COVID-19 disease, requiring ICU admission and may be responsible of cognitive impairment in the long term.

Our study confirms the presence of PNS involvement in COVID-19 patients, with a higher frequency in more severe patients. Others have described different kinds of manifestations, from Guillain Barrè syndrome, to cranial nerve or other nerve mononeuropathies, partial or complete brachial plexus inflammatory involvement and muscle inflammation ([28], as a review). Such clinical pictures are not COVID-19 specific, being similar to those observed in other viral and systemic diseases. As described by Andalib et al. [28], we also found that the PNS involvement was greater in patients with severe condition (13%), when compared to patients with mild/moderate COVID-19 (approximately 1%).

In conclusion, our study shows that, at a four-month follow-up, a mild cognitive impairment with the characteristics of a diffuse encephalopathy, with a preserved MMSE and a greater impairment in executive functions, is more frequent in COVID-19 patients who were treated in ICU. This impairment is not apparently related to either the severity of hypoxia at ICU admission, nor to the associated hypertension and diabetes, but is more severe in older patients and independent from the length of follow up.

Our study has some limitations: the larger sample of non-ICU vs. ICU patients, the lack of brain imaging, as well as of immunological and CSF analyses, which would have been useful to understand the pathophysiological mechanisms.

Future studies including more clinical groups of previous COVID-19 patients will be useful to confirm our findings and to better investigate the origin of either neurological or cognitive deficits in the acute and post-acute phase of the disease. Large-scale multidisciplinary collaborations, data repositories and specific projects will be needed [29], to better describe the neurological sequelae of specific populations of post-COVID-19 patients and reliably address their health-care needs. Finally, collaboration with critical care specialists, expert of Post Intensive Care Syndrome, will be essential to better understand the causes of these neurocognitive sequelae [30].

References

[1] A. Carfì, R. Bernabei, F. Landi, Gemelli Against COVID-19 Post-Acute Care Study Group, Persistent symptoms in patients after acute COVID-19, JAMA 324 (6) (2020) 603–605, https://doi.org/10.1001/jama.2020.

[2] C. Huang, L. Huang, Y. Wang, et al., 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study, Lancet 397 (2021) 220–232, https://doi.org/10.1016/S0140-6736(20)32656-8.

[3] C. Del Rio, M.F. Collins, P. Malani, Long-term health consequences of COVID-19, JAMA 324 (17) (2020) 1723–1724, https://doi.org/10.1001/jama.2020.19719.

[4] Morin, The Writing Committee for the COMEBAC Study Group, et al., Four-month clinical status of a cohort of patients after hospitalization for COVID-19, JAMA 325 (15) (2021) 1525–1534, https://doi.org/10.1001/jama.2021.3331.

[5] M.W. Tenforde, S.S. Kim, C.J. Lindsell, CDC COVID-19 Response Team, IVY Network Investigators, et al., Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network: United States, MMWR Morb. Mortal. Wkly Rep. 69 (30) (2020) 993–998, https://doi.org/10.15585/mmwr.mm6930e1.

[6] F. Callard, E. Perego, How and why patients made Long Covid, Soc. Sci. Med. 268 (2021), 113426, https://doi.org/10.1016/j.socscimed.2020.113426.

[7] Graham El, J.R. Clark, Z.S. Orban, et al., Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 “long haulers”, Ann. Clin. Transl. Neurol. 8 (5) (2021) 1073–1085, https://doi.org/10.1002/acn3.51350.

[8] I.J. Koralnik, K.L. Tyler, COVID-19: a global threat to the nervous system, Ann. Neurol. 88 (1) (2020) 1–11, https://doi.org/10.1002/ana.25807.

[9] The Lancet Neurology, Long COVID: understanding the neurological effects, Lancet Neurol. 20 (4) (2021) 247, https://doi.org/10.1016/S1474-4422(21)00059-4.

[10] F. Mattioli, C. Stampatori, F. Righetti, et al., Neurological and cognitive sequelae of Covid-19: a four month follow up, J. Neurol. (2021), https://doi.org/10.1007/s00415-021-10579-6.

[11] S.H. Chou, E. Beghi, R. Helbok, et al., Global incidence of neurological manifestations among patients hospitalized with COVID-19—a report for the GCS-NeuroCOVID consortium and the ENERGY consortium, JAMA Netw. Open 4 (5) (2021), e2112131, https://doi.org/10.1001/jamanetworkopen.2021.12131 (.

[12] M.F. Folstein, L.N. Robins, J.E. Helzer, The mini-mental state examination, Arch. Gen. Psychiatry 40 (7) (1983) 812.

[13] Pfoh, et al., Cognitive screening among acute respiratory failure survivors: a cross-sectional evaluation of the Mini-Mental State Examination, Crit. Care 19 (1) (2015) 220 (PMID: 25939482).

[14] M.D. Lezak, Neuropsychological Assessment, 3rd ed., Oxford University Press, 1995.

[15] S.J. Camp, V.L. Stevenson, A.J. Thompson, et al., Cognitive function in primary progressive and transitional progressive MS: a controlled study with MRI correlates, Brain 122 (1999) 1342–1348.

[16] G. Novelli, C. Papagno, E. Capitani, M. Laiacona, Tre test clinici di ricerca e produzione lessicale, in: Taratura su sogetti normali. Archivio di psicologia, neurologia e psichiatria, 1986.

[17] P. Caffara, Vezzadini, et al., Rey-Osterrieth complex figure: normative values in an italian population sample, Neurol. Sci. 22 (2002) 443–447.

[18] D.C. Delis, J.H. Kramer, E. Kaplan, B.A. Ober, California Verbal Learning Test, Second Edition (CVLT-II), Psychological Corporation, San Antonio, TX, 2000.

[19] S.J. Rosenberg, J.J. Ryan, A. Prifitera, Rey auditory-verbal learning test performance of patients with and without memory impairment, J. Clin. Psychol. 40 (3) (2009) 785–787.

[20] R.S. Keefe, T.E. Goldberg, P.D. Harvey, et al., The brief assessment of cognition in schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery, Schizophr. Res. 68 (2–3) (2004) 283–297.

[21] V.G. Puelles, M. Lütgehetmann, M.T. Lindenmeyer, et al., Multiorgan and renal tropism of SARS- CoV-2, N. Engl. J. Med. 383 (6) (2020) 590–592, https://doi.org/10.1056/NEJMc2011400.

[22] I.H. Solomon, E. Normandin, S. Bhattacharyya, et al., Neuropathological features of Covid-19, N. Engl. J. Med. 383 (2020) 989–992.

[23] A. Pezzini, A. Padovani, Lifting the mask on neurological manifestations of COVID-19, Nat. Rev. Neurol. 16 (2020) 636–664.

[24] J.A. Hosp, A. Dressing, G. Blazhenets, et al., Cognitive impairment and altered cerebral glucose metabolism in the subacute stage of COVID-19, Brain 144 (4) (2021) 1263–1276. https://academic.oup.com/brain/article/144/4/1263/6209743.

[25] S.F. Farhadian, D. Seilhean, S. Spudich, Neuropathogenesis of acute coronavirus disease 2019, Curr. Opin. Neurol. 34 (2021) 417–422, https://doi.org/10.1097/WCO.0000000000000944.

[26] Y. Zhou, T. Han, J. Chen, et al., Clinical and autoimmune characteristics of severe and critical cases of COVID 19, Clin. Transl. Sci. 13 (2020) 1077–1086.

[27] E. Song, C.M. Bartley, R.D. Chow, et al., Divergent and self reactive immune responses in the CNS of COVID-19 patients with neurological symptoms, Cell. Rep.

Med. 18;2 (5) (2021) 100288, https://doi.org/10.1016/j.xcrm.2021.100288 (Epub 2021 May 3).
[28] S. Andalib, et al., Peripheral nervous system manifestations associated with COVID-19, Curr. Neurol. Neurosci. Rep. 21 (2021) 9, https://doi.org/10.1007/s11910-021-01102-5.
[29] M. Burke, C. Del Rio, Long COVID has exposed medicine's blind-spot, Lancet (2021), https://doi.org/10.1016/S1473-3099(21)00333-9.
[30] P.P. Pandharipande, T.D. Girard, J.C. Jackson, et al., Long-term cognitive impairment after critical illness, NEJM 369 (14) (2013) 1306–1316, https://doi.org/10.1056/NEJMoa1301372.