Brain, Behavior, & Immunity - Health 9 (2020) 100163

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Full Length Article

Cognitive profile following COVID-19 infection: Clinical predictors leading to neuropsychological impairment

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ARTICLE INFO

Keywords:
COVID-19
Coronavirus
Neurological manifestations
Cognitive impairment
Neuropsychology

ABSTRACT

Background: Cognitive manifestations associated with the severity of a novel coronavirus (COVID-19) infection are unknown. An early detection of neuropsychological manifestations could modify the risk of subsequent irreversible impairment and further neurocognitive decline.

Methods: In our single-center cohort study, we included all consecutive adult patients, aged between 20 and 60 years old with confirmed COVID-19 infection. Neuropsychological assessment was performed by the same trained neuropsychologist from April, 22nd through June 16th, 2020. Patients with previous known cognitive impairment, any central nervous system or psychiatric disease were excluded. Demographic, clinical, pharmacological and laboratory data were extracted from medical records.

Results: Thirty-five patients met inclusion criteria and were included in the study. Patients presenting headache, anosmia, dysgeusia, diarrhea and those who required oxygen therapy had lower scores in memory, attention and executive function subtests as compared to asymptomatic patients. Patients with headache and clinical hypoxia scored lower in the global Cognitive Index ($P = 0.002$, $P = 0.010$). A T *score* lower than 30 was observed in memory domains, attention and semantic fluency (2 [5.7%]) in working memory and mental flexibility (3 [8.6%]) and in phonetic fluency (4 [11.4%]). Higher scores in anxiety and depression ($P = 0.047$, $P = 0.008$) were found in patients with cognitive complaints.

Conclusions: In our cohort of COVID-19 patients neurologic manifestations were frequent, including cognitive impairment. Neurological symptoms during infection, diarrhea and oxygen therapy were risk factors for neurocognitive impairment. Cognitive complaints were associated with anxiety and depression.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the etiologic agent of the current rapidly growing outbreak of coronavirus disease (COVID-19). Common symptoms include fever, dry cough, fatigue and dyspnea, whereas respiratory failure and subsequent pneumonia frequently leads to hospitalization. Neurological manifestations are being recognized increasingly. The most frequent being headache, myalgias or loss of burst and smell (Mao et al., 2020a). These manifestations can be considered as direct effect of the virus on the central nervous system (CNS), para-infectious or post-infectious immune–mediated disease, and neurological complications of the systemic effects of COVID-19 (Li et al., 2020; Helms et al., 2020). Similarly to SARS-CoV, COVID-19 virus uses angiotensin 2 (ACE2) to enter cells. It raises the necessity for studies of ACE2 expression in the CNS to determine the direct impact of COVID-19 on brain tissue (Baig et al., 2020). Hoffmann et al. (2020) provided evidence that host cell entry of SARS-CoV-2 depends on the SARS-CoV receptor ACE2 providing key insights into the first step of the infection and viral entry into the cells.

Mao et al. (2020b) reported 36.4% COVID-19 patients had neurological manifestations, mainly those patients with severe symptoms. Several hospital series described myalgias, headaches, dizziness, confusion and

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https://doi.org/10.1016/j.bbih.2020.100163
Received 5 September 2020; Received in revised form 15 October 2020; Accepted 21 October 2020
Available online 22 October 2020

epileptic seizures (Li et al., 2020; Wu et al., 2020; Chen et al., 2020; Guan et al., 2020; Arentz et al., 2020). Cases from mild-to-moderate COVID-19 associated encephalopathy and stroke were published, probably due to the prothrombotic and proinflammatory state of COVID-19 infection. It is well known the impact that CNS viral infections (Warren-Gash et al., 2019), inflammatory processes (Sartori et al., 2012) and cerebral hypoxia (McMorris et al., 2017) have on cognitive functions producing transient or permanent cognitive impairment. Limbic and associated brain structures such as the hippocampus and basal ganglia contain more enzymes that are involved in inflammatory responses than other areas. Therefore, there is an increased risk of developing deficits in neurocognitive processes like memory, attention and emotion (Sartori et al., 2012; Raz and Rodrigue, 2006). Patients with chronic hypoxia due to pulmonary diseases, may have worst performance on attention, executive functions and processing speed tests. Cognitive impairment correlates with the severity of pulmonary disease and support the diagnosis of subcortical type encephalopathy (Areza-Fegyveres et al., 2010). Cognitive impairment as a result of acquired brain damage is a common cause of complaints in neurological units, as it causes difficulties in performing day-to-day activities, including working difficulties, with great functional and emotional repercussion not only for patient himself but in their family environment.

There are no studies to our knowledge on the co-existence and clinical definition of cognitive impairment related to COVID-19 infection. As COVID-19 outbreak may directly impact on CNS, it is likely that we will face more neurocognitive complaints once severe respiratory syndrome is resolved. It is of great scientific and clinical relevance to describe COVID-19 related cognitive symptoms due to its possible reversibility and the differences from the impairment caused by neurodegenerative disease. In this study, we aimed to evaluate the impact of COVID-19 on neurocognitive performance.

2. Methods

2.1. Study design and participants

This is our cohort study, we included consecutive adult patients evaluated in Hospital Universitari MútuaTerrassa (HUMT) from April 21 (date of first specimen assessed) to June 16, 2020. All patients included in the study had SARS-Cov-2 infection confirmed by positive PCR from nasopharyngeal swab and/or positive serology. Patients aged from 24 to 60 years old. Subjects with previous cognitive impairment and any other CNS disease were excluded. The study was approved by the local ethic committee and all subjects signed the informed consent.

2.2. Data collection and definitions

Clinical data was collected prospectively in HUMT and we retrospectively reviewed electronic health records database for all patients with laboratory-confirmed SARS-CoV-2 infection. Demographic data, comorbidities, blood test results that included ferritin and D-Dimer, symptoms and signs at presentation, complications, treatment, previous cognitive impairment or cognitive complaints after infection and outcomes were collected and evaluated. Complications included hypoxic respiratory failure, encephalitis and stroke. Outcomes include length of stay, length of symptoms, need of invasive mechanical ventilation and discharge disposition. To assess cognitive impairment, a set of subtests was selected to create a Neuropsychological battery specific for this population. All tests are validated in our population and are used internationally. The battery included: Test de Aprendizaje Verbal España-Complutense (TAVEC) with three lists for the Learning, Interference and Recognition to assess verbal memory; Visual Reproduction of the Wechsler Memory Scale –IV (WMS-IV), Digits forward and Backward, Letter and Numbers, Trail Making Test A and B (TMT), Symbol Digit Modalities Test (SDMT), Stroop, Phonemic and Semantic fluency and Boston Naming Test from the NEURONORMA project (NN). Scores used for the analysis of the results were the standardized notes, according to normalized data in our environment, thus correcting the effects of the subjects' age and education, as well as giving the data greater compliance with the Normal Distribution, specifically used the T note (PT) (mean 50 points and standard deviation of 10 points). Additionally, a total cognitive performance score was created by obtaining an arithmetic mean of the standardized scores of the different cognitive tests used, called the Cognitive Index (ICog). Also Hospital Anxiety and Depression Scale (HAD) was administered to assess symptoms of anxiety and depression. All the assessments were performed between 10 and 35 days from hospital discharge by the same trained neuropsychologist and cognitive evaluation lasted approximately 1 h.

2.3. Statistical analysis

In a first level of analysis the sample data and cognitive results were described assuming Normal Distribution, knowing its performance in larger samples and being standardized in our population. Standardized punctuations (T scores) for different cognitive tests were expressed in frequencies as well as the Cognitive Index as an expression of pathological results in those with scores equal to or less than 30 in their T score (corresponding to 2 standard deviations or less). In a second level of analysis, inferential tests were performed to compare cognitive performance according to other characteristics of the sample of clinical relevance. Comparisons between cohorts were analyzed using the t-Student Test (independent variables), and Levene test was used to assume equal variances or not on groups of comparison analysis. Due to sample size, comparisons between groups have been made only if they had more than 5 subjects per group (assuming a minimum representation of subjects per group of 15%). Statistical analyses were performed using R. CRAN. *Oficina de software libre (CIXUG)*. Spanish National Research Network. http://cran.es.r-project.org/

2.4. Data availability

All study data, including raw and analyzed data and materials will available from the corresponding author on reasonable request.

3. Results

3.1. Demographic and clinical characteristics

Between April and June 2020, 454 patients tested positive for SARS-CoV-2 at HUMT. Of these patients, subjects older than 60 were excluded from the study to avoid cognitive impairment due to age-related cognitive decline. Patients with previous cognitive impairment and any other CNS or psychiatric affection were also excluded from the study. Neuropsychological study was performed between 10 and 35 days after hospital discharge to have the most recent possible cognitive profile related to the infection.

A total of thirty-five patients were included in the study. Their demographic and clinical characteristics are described in Table 1. 19 subjects were female (54.3%) with mean (SD) age of 47.6 (8.9) years. Most common symptoms at onset of illness were fever (16 [45.7%]), cough (10 [28.6%]), fatigue (6 [17.1%]), headache (2 [5.7%]) and myalgias (1 (2.9%]). In the course of the infection, thirty-one patients (88.6%) had

Table 1
Demographic and clinical characteristics of patients with COVID-19 infection.

Characteristics	Minimum	Maximum	Mean	Std. Deviation
Age, y	24	60	47.6	8.9
Education, y	6	18	12.6	4.6
Hospital discharge, d	10	40	25.9	7.7
Hospitalization, d	0	30	10.8	9.2
Total symptoms, d	5	40	18.8	10.1
D-Dímer ng/mL	241.0	5568.0	1655.3	1833.1
Ferritin ng/mL	21.2	5498.7	955.0	1258.5

Abbreviations: COVID-19, coronavirus disease 2019.

cough, thirty-four (97.1%) had fever, thirty (85.7%) had myalgias, thirty-one (88.6%) had fatigue, twenty-two (62.9%) had headache, twenty (57.1%) had anosmia, twenty (57.1%) had dysgeusia, thirty-three (94.3%) had breathing difficulties, fourteen (40%) had diarrhea, four (11.4%) had skin affection, seven (20%) required Intensive Care Unit (ICU), twenty-one (60%) required oxygen. Mean hospital stay was 10.86 days and mean days of symptoms length was 18.8 days.

Laboratory findings showed that males had higher levels of ferritin than females (mean [SD] 1765.9 vs. 346.9; P = 0.010) and higher levels of D-Dimer values (mean [SD] 2415.5 vs 1047.2 although it wasn't statistically significant; P = 0.067). For patients that required ICU care, higher levels of ferritin (P = 0.034) and D-Dimer (P = 0.001) were found. Same results were found for patients that needed oxygen therapy during hospitalization, with higher results in D-Dimer (P = 0.031) and ferritin (P = 0.024).

3.2. Neuropsychological findings

Neuropsychological characteristics are described in Table 2. The punctuation for each test is expressed in T score. To note, of all patients, twelve (34.3%) had cognitive complaints.

Pathological scores (PT ≤ 30) were seen in TAVEC-1 (2 [5.7%]), TAVEC-5 (2 [5.7%]), TAVECTotal (1 [2.9%]), TAVEC-B (2 [5.7%]), TAVEC-IMR (1 [2.9%]), TAVEC-IMRSC (2 [5.7%]), TAVEC-DFR (2 [5.7%]), TAVEC-DFRSC (3 [8,6%]), TAVEC-REC (2 [5.7%]), Inverse Digits (3 [8,6%]), TMT-A (1 [2.9%]), TMT-B (3 [8,6%]), SDMT (2 [5.7%]), Stroop Color (1 [2.9%]), Stroop Interference (1 [2.9%]), Semantic Fluency (2 [5.7%]), Phonemic Fluency (4 [11,4%]), FCRO copy (1 [2.9%]), BNT (1 [2.9%]).

An analysis of neuropsychological scores was performed just for the clinical variables with N > 5 for group. For this reason, fever, cough, fatigue, myalgias and skin affection, were excluded from the analysis (practically all subjects presented these conditions, understood as part of the pathological clinic). Table 3 showed neuropsychological findings for the subtests that were statistically significant. Patients presenting neurological symptoms such as headache, anosmia and dysgeusia were associated with lower scores in working memory (P = 0.031, P = 0.031,

Table 2
Neuropsychological characteristics of patients with COVID-19 infection.

Characteristics	Minimum	Maximum	Mean	Std. Deviation
TAVEC-1 (PT)	30.0	70.0	48.6	9.7
TAVEC–5 (PT)	30.0	70.0	50.9	9.8
TAVECTotal (PT)	30.0	70.0	51.4	8.1
TAVEC-B (PT)	30.0	60.0	46.9	8.3
TAVEC-IMR (PT)	30.0	70.0	50.6	10.0
TAVEC-IMRSC (PT)	30.0	70.0	49.7	9.8
TAVEC-DFR (PT)	30.0	70.0	50.9	10.7
TAVEC-DFRSC (PT)	30.0	70.0	50.3	10.7
TAVEC-REC. (PT)	30.0	60.0	52.9	8.4
WMS-IMR (PT)	35.0	57.5	46.0	5.6
WMS-DFR (PT)	37.5	65.0	48.9	6.9
Digits Forward (PT)	32.5	60.0	46.9	6.2
Digits Backwards (PT)	30.0	57.5	45.7	7.5
Letter&Numbers (PT)	32.5	65.0	45.1	5.8
TMT-A (PT)	30.0	62.5	45.9	7.0
TMT-B (PT)	27.5	57.5	42.9	8.2
SDMT (PT)	30.0	65.0	43.9	7.0
Stroop Lecture (PT)	32.5	57.5	44.1	7.7
Stroop Color (PT)	30.0	57.5	44.2	6.4
Stroop Int. (PT)	30.0	57.5	45.1	6.8
Semantic Fluency (PT)	27.5	60.0	47.6	8.1
Phonemic Fluency(PT)	26.7	57.5	43.7	7.4
FCRO copy (PT)	30.0	67.5	54.1	11.7
BNT (PT)	27.5	67.5	47.1	7.2
Cognitive Index (PT)	38.0	60.6	48.0	45.4
HAD Anxiety (PD)	0	20	7.6	4.6
HAD Depression (PD)	0	12	4.4	3.3

Abbreviations: COVID-19, coronavirus disease 2019; TAVEC-1, Test de Aprendizaje Verbal España-Complutense learning 1; TAVEC–5, Test de Aprendizaje Verbal España-Complutense learning 5; TavecTotal, Test de Aprendizaje Verbal España-Complutense sum of learning; TAVEC-B, Test de Aprendizaje Verbal España-Complutense learning B; TAVEC-IMR, Test de Aprendizaje Verbal España-Complutense Immediate Recall; TAVEC-IMRSC, Test de Aprendizaje Verbal España-Complutense Immediate Recall Semantic Clue; TAVEC-DFR, Test de Aprendizaje Verbal España-Complutense Deferred Free Recall; TAVEC-DFRSC, Test de Aprendizaje Verbal España-Complutense Deferred Free Recall Semantic Clue; TAVEC-REC, Test de Aprendizaje Verbal España-Complutense Recognition; WMS-IMR, Visual Reproduction of the Wechsler Memory Scale –IV Immediate Recall; WMS-DFR, Visual Reproduction of the Wechsler Memory Scale –IV Deferred Free Recall; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B; SDMT, Symbol Digit Modalities Test; BNT, Boston Naming Test; HAD, Hospital Anxiety and Depression scale; PT, T score; PD, direct score.

Table 3
Neuropsychological findings related to clinical characteristics.

Symptom/Subtest	Leven's Test for Equality of Variances		t-test for Equality of Means	
	F	Sig.	t	Sig.
CEFALEA (N = 22)				
TAVEC-1	.736	0.389	2.221	0.033
TAVEC-Total	.752	0.392	2.937	0.006
TAVEC-B	.029	0.866	2.805	0.008
TAVEC-IMR	.824	0.371	2.331	0.026
Digits Forward	.094	0.761	3.392	0.002
Digits Backwards	.160	0.692	2.261	0.031
Letter&Number	.173	0.680	2.177	0.037
TMT-B	.254	0.617	2.488	0.018
SDMT	.828	0.369	2.727	0.010
Stroop Lecture	1.155	0.291	2.685	0.011
Phonetic fluency	1.399	0.245	2.211	0.034
Cognitive Index	.667	0.420	3.475	0.002
ANOSMIA (N = 20)				
Digits Backwards	1.802	0.189	2.259	0.031
DYSGEUSIA (N = 20)				
Digits Backwards	1.802	0.189	2.259	0.031
BNT	.043	0.837	3.596	0.001
DIARRHEA (N = 14)				
WMS-DFR	.341	0.563	2.082	0.045
Digits Backwards	.183	0.671	2.470	0.019
Letter&Number	3.522	0.069	2.102	0.043
Stroop Color	5.504	0.025	−2.370[a]	0.032
OXYGEN (N = 21)				
TAVEC-IMR	.053	0.820	2.270	0.030
WMS-DFR	.974	0.331	3.046	0.005
Digits Forward	.615	0.439	3.379	0.002
Digits Backwards	2.383	0.132	2.185	0.036
Letter&Number	.071	0.791	2.320	0.027
TMT-A	.159	0.693	2.193	0.035
TMT-B	.491	0.488	2.778	0.009
SDMT	.366	0.550	2.281	0.029
Stroop Lecture	3.018	0.092	2.403	0.022
Stroop Color	1.292	0.264	2.090	0.045
Stroop Interference	.049	0.825	2.431	0.021
Semantic Fluency	6.923	0.013	2.601[a]	0.014
Cognitive Index	1.426	0.241	2.727	0.010
ICU (N = 7)				
TMT-B	.026	0.873	2.177	0.037
COGNITIVE COMPLAINTS (N = 12)				
HAD Anxiety	5.266	0.028	−2.172[a]	0.047
HAD Depression	.878	0.356	−2.817	0.008

Abbreviations: ICU, Intensive Care Unit; TAVEC-1, Test de Aprendizaje Verbal España-Complutense learning 1; TavecTotal, Test de Aprendizaje Verbal España-Complutense sum of learning; TAVEC-B, Test de Aprendizaje Verbal España-Complutense learning B; TAVEC-IMR, Test de Aprendizaje Verbal España-Complutense Immediate Recall; WMS-DFR, Visual Reproduction of the Wechsler Memory Scale –IV Deferred Free Recall; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B; SDMT, Symbol Digit Modalities Test; BNT, Boston Naming Test; HAD, Hospital Anxiety and Depression scale. F, Levene Test; t., Student Test; Sig., Significance; values indicate differences between patients with symptoms and without symptoms. N represents subjects with symptoms. Table showed subtests with less than 0.05 which was considered statistically significant.

[a] Non-equal variances are assumed.

P = 0.031) respectively compared with patients without this symptoms. Patients presenting headache showed also lower scores in memory coding (P = 0.006), attention (P = 0.002), complex working memory (P = 0.037), process speed (P = 0.010), executive function (P = 0.034, P = 0.018) and in the global Cognitive Index (P = 0.002). Patients with dysgeusia had also lower scores in denomination (P = 0.001).

Patients who presented diarrhea showed lower scores in delayed visual memory (P = 0.045), working memory (P = 0.019 and complex working memory (P = 0.043). For patients that required ICU care, lower punctuations in executive function were found (P = 0.037) whereas patients that required oxygen therapy showed lower punctuations in verbal memory (P = 0.030), visual memory (P = 0.005), attention (P = 0.002), working memory (P = 0.036), complex working memory (P = 0.027), process speed (P = 0.035, P = 0.029), executive function (P = 0.009, P = 0.014) and the global Cognitive Index (P = 0.010).

No differences in neuropsychological tests were found between patients that expressed cognitive deficits after COVID-19 infection than patients who didn't. Nevertheless, higher scores in Anxiety and Depression test (P = 0.047, P = 0.008 respectively) were found in the group with cognitive complaints.

4. Discussion

Association between COVID-19 and cognitive impairment was not previously reported. Considering that COVID-19 had known neurotropism and that cognitive deficits are seen in other viral infections, we believed that the association is very likely.

We found COVID-19 infection profile to be consistent with that described in general population. In our cohort, fever was the predominant symptom in all patients, followed by cough, myalgias, fatigue and headache as described in previous studies (Li et al., 2020; Wu et al., 2020; Chen et al., 2020; Guan et al., 2020; Arentz et al., 2020). Males showed higher levels of D-Dimer and ferritin than females. According to other studies, COVID-19 severe infection was more frequent in males possibly as result of their higher ACE2 levels (Sama et al., 2020).

Similar to other respiratory viruses, SARS-CoV-2 may enter the CNS through the hematogenous or retrograde neuronal route, supported by the fact that twenty (57%) of the patients in this study had smell impairment. Neurological symptoms such as headache, loss of smell and taste were strongly associated with impairment in several subtests including attention, memory and executive function domains. Of the above symptoms, headache was the neurological symptom frequently associated with poor performance in neuropsychological tests. This phenomenon may be indicative of the potential COVID-19 CNS invasion capacity as described in other studies (Mao et al., 2020a; Li et al., 2020). We also found cognitive impairment in patients that required oxygen therapy during hospitalization; this could be explained by the continuous hypoxia caused by pulmonary disease related to COVID-19 infection (Areza-Fegyveres et al., 2010). Headache and oxygen therapy independently were the main variables strongly related to cognitive impairment. In patients with these symptoms, global Cognitive Index was impaired. Patients presenting diarrhea during infection had worse performance in neuropsychological test. We did not record whether diarrhea was caused by the infection or if it was secondary to pharmacological treatment. It would be convenient to take this information into account for future studies.

In our hospital cohort, twelve (34.3%) patients had cognitive complaints after COVID-19 infection. No differences in cognition were reported as compared to patients with no complaints but they had significantly higher scores in anxiety and depression. Patients with cognitive complaints related them to attention deficits and anomia. Emotional distress, such as anxiety, depression and insomnia could play a role in subjective cognitive complaints. These findings emphasize the importance of an early detection of anxiety and depression in order to avoid later cognitive complaints in COVID-19 patients.

5. Limitations

This study has several limitations. Only 35 patients were included. It would be better to include more patients in order to assess potential cognitive differences associated with other symptoms such as myalgia or fatigue. It is important to note that older population were excluded to avoid age-related cognitive impairment. Neuropsychological assessment was performed in early period after hospitalization in order to have the most recent possible cognitive profile related to the infection and its possible temporal relationship with the resolution. Some of the data was extracted from the electronical medical records; some manifestations might not be captured if they were too mild or not easily referred by the patient, such as taste and smell impairment or diarrhea. We probably missed some of the patients with MRI hypoxic lesions. Future studies should include advanced neuroimaging and a long term follow up assessment of the deficits to determine whether this could precipitate the onset of neurodegenerative or cerebrovascular disease.

6. Conclusions

Patients having COVID-19 infection could have cognitive impairment shortly after hospital discharge. Presence of neurological symptoms during the infection such as headache, anosmia and dysgeusia were the main risk factors for cognitive impairment related with attention, memory and executive function. The need for oxygen therapy and diarrhea were also associated with memory, attention and executive function deficits. Anxiety and depression were associated with cognitive complaints, although no impairment was evidenced on neuropsychological tests in these patients.

Our data describe important new clinical information that could help clinicians raise awareness of the appearance of cognitive manifestations in patients with COVID-19 infection. Clinicians should consider the identification and assessment of these patients and a long term follow up to prevent further impairment.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure

M. Almeria reports no disclosures relevant to the manuscript. JC. Cejudo reports no disclosures relevant to the manuscript. J. Sotoca reports no disclosures relevant to the manuscript. J. Deus reports no disclosures relevant to the manuscript. J. Krupinski reports no disclosures relevant to the manuscript.

Declaration of competing interest

The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

Acknowledgements

The authors thank the patients and all the physicians and health personnel of HUMT involved in the care of these patients during COVID-19 pandemic.

The Agency of University and Research Funding Management of the Catalonia Government participated in the context of Research Groups SGR2019/1198 (J. Deus).

EPIGENESIS Project. Instituto de Salud Carlos III. Pl17/02089 (J. Krupinski).

References

Arentz, M., Yim, E., Klaff, L., Lokhandwala, S., Riedo, F.X., Chong, M., Lee, M., 2020. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. Jama 323 (16), 1612–1614. https://doi:10.1001/jama.2020.4326.

Areza-Fegyveres, R., Kairalla, R.A., Carvalho, C.R., Nitrini, R., 2010. Cognition and chronic hypoxia in pulmonary diseases. Dementia & Neuropsychol. 4 (1), 14–22. https://doi:10.1590/S1980-57642010DN40100003.

Baig, A.M., Khaleeq, A., Ali, U., Syeda, H., 2020. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. ACS Chem. Neurosci. 11 (7), 995–998. https://doi.org/10.1021/acschemneuro.0c00122.

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Yu, T., 2020. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395 (10223), 507–513. https://doi:10.1016/S0140-6736(20)30211-7.

Guan, W.J., Ni, Z.Y., Hu, Y., Liang, W.H., Ou, C.Q., He, J.X., Du, B., 2020. Clinical characteristics of coronavirus disease 2019 in China. N. Engl. J. Med. 382 (18), 1708–1720. https://doi:10.1056/NEJMoa2002032.

Helms, J., Kremer, S., Merdji, H., Clere-Jehl, R., Schenck, M., Kummerlen, C., Anheim, M., 2020. Neurologic features in severe SARS-CoV-2 infection. N. Engl. J. Med. 382, 2268–2270. https://doi:10.1056/NEJMc2008597.

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Müller, M.A., 2020. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181 (2), 271–280. https://doi:10.1016/j.cell.2020.02.052.

Li, Y.C., Bai, W.Z., Hashikawa, T., 2020. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J. Med. Virol. 92 (6), 552–555. https://doi:10.1002/jmv.25728.

Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., Miao, X., 2020a. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 77 (6), 683–690. https://doi:10.1001/jamaneurol.2020.1127.

Mao, L., Wang, M., Chen, S., He, Q., Chang, J., Hong, C., Li, Y., 2020b. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. https://doi:2020.02.22.20026500.

McMorris, T., Hale, B.J., Barwood, M., Costello, J., Corbett, J., 2017. Effect of acute hypoxia on cognition: a systematic review and meta-regression analysis. Neurosci. Biobehav. Rev. 74, 225–232. https://doi:10.1016/j.neubiorev.2017.01.019.

Raz, N., Rodrigue, K.M., 2006. Differential aging of the brain: patterns, cognitive correlates and modifiers. Neurosci. Biobehav. Rev. 30 (6), 730–748. https://doi:10.1016/j.neubiorev.2006.07.001.

Sama, I.E., Ravera, A., Santema, B.T., van Goor, H., Ter Maaten, J.M., Cleland, J.G., Dickstein, K., 2020. Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin–angiotensin–aldosterone inhibitors. Eur. Heart J. 41 (19), 1810–1817. https://doi:10.1093/eurheartj/ehaa373.

Sartori, A.C., Vance, D.E., Slater, L.Z., Crowe, M., 2012. The impact of inflammation on cognitive function in older adults: implications for health care practice and research. J. Neurosci. Nurs. 44 (4), 206. http://doi:10.1097/JNN.0b013e3182527690.

Warren-Gash, C., Forbes, H.J., Williamson, E., Breuer, J., Hayward, A.C., Mavrodaris, A., Smeeth, L., 2019. Human herpesvirus infections and dementia or mild cognitive impairment: a systematic review and meta-analysis. Sci. Rep. 9 (1), 1–10. https://doi.org/10.1038/s41598-019-41218-w.

Wu, Y., Xu, X., Chen, Z., Duan, J., Hashimoto, K., Yang, L., Yang, C., 2020. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav. Immun. 87, 18–22. https://doi.org/10.1016/j.bbi.2020.03.031.