COVID-19

Original article

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Cognitive impairment in COVID-19 patients and its relation to laboratory data

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Abstract

Introduction: Neuropsychological manifestations are increasingly reported in patients with COVID-19, but the subject is poorly understood and our knowledge about cognitive impairment is limited. This study aimed to investigate neuropsychological involvement of COVID-19 and its relation to laboratory data.
Material and methods: This study was conducted among patients admitted to a tertiary medical center in Iran, in the period March 2020 to March 2021. Neuropsychiatric assessments were carried out by the Addenbrooke's Cognitive Examination (ACE) test in all patients and interpreted by a specialist. It was performed using the Persian version of ACE in six domains consisting of attention, orientation, memory, language, visual perception and visuospatial skills. Laboratory data were assessed among all patients. Statistical analyses were performed using SPSS.
Results: Among 114 patients with COVID-19, the mean age was 48.46 ±13.61 years, and the male/female ratio was 1.32. The mean values of some abnormal laboratory data were: erythrocyte sedimentation rate (ESR) 57.2 ±29.8, C-reactive protein (CRP) 81.7 ±59.8 and D-dimer 459.3 ±395.4. Cognitive impairment was detected in 41 patients (63%). The mean score of ACE was 80.68 ±19.29. Statistical analysis showed correlations between total result of the ACE test and laboratory findings that were not statistically significant.
Conclusions: In our study, no relation was found between laboratory test results and the overall cognitive examination score but statistical analysis showed a correlation between CRP and verbal fluency, between hemoglobin level and language and visuospatial domains, and also between total level of bilirubin and memory. These relations may suggest that we should follow the neurocognitive features in COVID-19 patients earlier.

Key words: COVID-19, cognitive impairment, neuropsychological involvement, laboratory data.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) globally impacted healthcare systems with millions of deaths and many more infected patients. Mainly known for involvement of the respiratory system, it is now evident that COVID-19 is a multi-organ disease. Studies have demonstrated the involvement of gastrointestinal and cardiovascular systems and also involvement of the central and peripheral nervous system after this infection (Mao *et al*. 2020; Huang *et al*. 2020).

Neuropsychological manifestations are increasingly reported in patients with COVID-19 (Ellul *et al*. 2020; Varatharaj *et al*. 2020), commonly observed during the second week from the disease onset and among patients with the severe form of the disease (Mao *et al*. 2020; Paterson *et al*. 2020; Román *et al*. 2020; Koralnik and Tyler 2020). There are some reports demonstrating persistency of neuropsychological manifestations and cognitive impairment in the post-acute phase after recovery from respiratory symptoms (Negrini *et al*. 2021; Woo *et al*. 2020; Heneka *et al*. 2020).

Neuropsychological manifestations have been reported in 36.4% to 82.3% of hospitalized patients (Mao *et al*. 2020; Romero-Sánchez *et al*. 2020; Liotta *et al*. 2020). The most frequent are anosmia, ageusia, headache and myalgia (Mao *et al*. 2020). The most common forms of cognitive impairment during the acute and post-acute phase were decline in attention, memory, language and praxis abilities (Negrini *et al*. 2021; Sheng *et al*. 2005). Reports about persistency of these symptoms during the post-acute phase indicate the need for more studies on neuropsychological aspects of COVID-19. Based on our experience with severe acute respiratory syndrome (SARS) (Sheng *et al*. 2005), systemic inflammation has been suspected to be at least one of the pathways responsible for neuropsychological manifestations in COVID-19, and recent studies support this suspicion (Huang *et al*. 2020). Coronavirus can invade the central nervous system (CNS) through blood vessels and neuronal retrograde pathways, then brain injury and dysfunction of the cardiorespiratory center in the brainstem can occur and manifest as neurological symptoms and respiratory failure in infected animals and patients. Also, neurotropic RNA coronaviruses could disrupt the blood–brain barrier (BBB) and affect neuroimmune interactions (Han *et al*. 2021).

Confronted with the COVID-19 pandemic our main focus has been on treating respiratory involvement and reducing mortality. As the involvement of other organs unfolds over time, there will be many questions to be addressed. Neuropsychological involvement of COVID-19 is poorly understood and our knowledge about cognitive impairment is limited. Here we aimed to investigate neurocognitive involvement in COVID-19 and its relation to laboratory data and illness variables.

Material and methods

This prospective study was conducted among patients admitted to a tertiary medical center in Iran, in the period March 2020 to March 2021. Inclusion criteria were age over 18 years and a certain diagnosis of COVID-19. All patients underwent neurological and psychiatric examination by an expert neurosurgeon (A.P.). The COVID-19 diagnosis was confirmed by polymerase chain reaction (PCR) and spiral chest computed tomography (CT) scan under observation of an infectious disease specialist (A.H. & M.M.) and pulmonologist (M.P. & S.K.). Psychiatric disorder, intracranial lesions, history of surgery, and severe traumatic brain injury were our exclusion criteria.

Neuropsychiatric assessments were carried out by Addenbrooke's Cognitive Examination (ACE) test in all patients and interpreted by a specialist. It was performed using the Persian version of ACE in six domains consisted of attention, orientation, memory, language, visual perception and visuospatial skills (Pouretemad *et al*. 2009). Also, the test's cut-off point was 84; and an ACE score equal to or less than 84 was considered as some cognitive impairment (Pouretemad *et al*. 2009; Noone 2015).

Laboratory data and their normal range were as follows: white blood cells (WBC) 4.5-10.5 $\times 10^3$ cells/μl, hemoglobin (Hb) 13.5-18 g/dl, platelets (Plt) 150 000-400 000 cell/μl, neutrophils (Neut) 54-62%, lymphocytes (lymph) 25-33%, erythrocyte sedimentation rate (ESR) 0-18 mm/h, C-reactive protein (CRP) 0-10 mg/l, lactate dehydrogenase (LDH) ≥ 480 U/l, D-dimer ≤ 500 ng/ml, prothrombin time (PT) 11-13.5 seconds, partial thromboplastin time (PTT) 25-35 seconds, international normalized ratio (INR) 0.8-1.1, vitamin-D (Vit-D) 20-80 ng/ml, aspartate aminotransferase (AST) 5-38 U/l, alanine aminotransferase (ALT) 7-41 U/l, alkaline phosphatase (ALK-P) 44-270 IU/l, bilirubin total (Bili-T) 0-1.2 mg/dl, bilirubin direct (Bili-D) 0-0.3 mg/dl, blood urea nitrogen (BUN) 18-55 mg/dl, creatinine (Cr) 0.7-1.4 mg/dl, sodium (Na) 135-145 mEq/l and potassium (K) 3.5-5.5 mmol/l.

Statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, version 26.0.). Descriptive statistics, including frequency distributions, mean and standard deviation (SD), were calculated for all quantitative variables. To compare variable distributions, we used the chi-squared test for categorical variables, and applied Pearson's correlation test to measure the linear association of two variables. A p-value less than 0.05 was considered as significant.

Results

Among 114 patients with COVID-19, the mean age was 48.46 ±13.61 years, and the male/female ratio was 1.32. Demographic variables are shown in Table 1.

The mean abnormal laboratory data were as follows: ESR 57.2 ±29.8, CRP 81.7 ±59.8, LDH 751.1 ±375.1, D-dimer 459.3 ±395.4, AST 62.1 ±68.6, and ALT 53.1 ±48.1; the mean of others were in the normal range. Table 2 shows the laboratory findings.

Table 1. Demographic characteristics of patients with COVID-19

Variable		Frequency (*N* = 114), *n* (%)	ACE* test, mean ±SD	Frequency of cognitive impairment, *n* (%)	*P*-value
Sex	Male	65 (57)	83.95 ±17.83	18 (43.9)	0.03
	Female	49 (43)	76.33 ±20.46	23 (56.1)	
Handedness	Left	5 (4.4)	88.20 ±12.62	2 (4.9)	0.37
	Right	109 (95.6)	80.33 ±19.52	39 (95.1)	
Education	Under diploma	33 (29)	68.41 ±22.50	21 (51.2)	0.01
	Diploma or over	81 (71)	85.89 ±15.12	20 (48.8)	
Smoking	No	97 (85.1)	81.72 ±17.52	35 (85.4)	0.32
	Yes	17 (14.9)	74.71 ±27.24	6 (14.6)	
Opioid	No	112 (98.2)	80.54 ±19.44	41 (100)	0.59
	Yes	2 (1.8)	88 ±2.83	0	
Dexamethasone administration	No	59 (52)	79.59 ±20.67	22 (53.7)	0.54
	Yes	55 (48)	81.80 ±17.84	19 (46.3)	

ACE – Addenbrooke's Cognitive Examination

Table 2. Laboratory data of patients with COVID-19

Variables	Mean ±SD	Abnormal, *n* (%)	Normal, *n* (%)
WBC	7.95 ±2.91	88 (77.2)	26 (22.8)
Hb	13.32 ±2.17	53 (46.5)	61 (53.5)
Plt	239.95 ±95.10	88 (77.2)	26 (22.8)
Neut	78.21 ±7.87	3 (2.6)	111 (97.4)
Lymph	16.39 ±7.09	16 (14)	98 (86)
ESR	60.39 ±25.07	8 (7)	106 (93)
CRP	78.21 ±54.14	5 (4.4)	106 (93)
LDH	76.21 ±331.19	87 (76.3)	27 (23.7)
D-dimer	452.85 ±320.92	75 (65.8)	39 (34.2)
PT	13.79 ±2.63	63 (55.3)	51 (44.7)
PTT	37.93 ±11.17	47 (41.2)	67 (58.8)
INR	1.12 ±0.25	74 (64.9)	40 (35.1)
AST	61.16 ±66.01	38 (33.3)	76 (66.7)
ALT	51.93 ±46.19	62 (54.4)	52 (45.6)
ALK-P	176.53 ±81.33	95 (83.3)	19 (16.7)
Bili-T	0.78 ±0.32	100 (96.5)	4 (3.5)
Bili-D	0.38 ±0.48	56 (49.1)	58 (50.9)
BUN	39.09 ±23.65	89 (78.1)	25 (21.9)
Cr	1.12 ±0.41	99 (86.8)	15 (13.2)
Na	137.08 ±11.57	74 (64.9)	40 (35.1)
K	4.28 ±0.60	101 (88.6)	13 (11.4)

WBC – white blood cells, Hb – hemoglobin, Plt – platelets, Neut – neutrophils, Lymph – lymphocytes, ESR – erythrocyte sedimentation rate, CRP – C-reactive protein, LDH – lactate dehydrogenase, PT – prothrombin time, PTT – partial thromboplastin time, INR – international normalized ratio, AST – aspartate aminotransferase, ALT – alanine aminotransferase, ALK-P – alkaline phosphatase, Bili-T – bilirubin total, Bili-D – bilirubin direct, BUN – blood urea nitrogen, Cr – creatinine, Na – sodium, K – potassium

Cognitive impairment was detected in 41 patients (63%). The mean score of ACE was 80.68 ±19.29 (executive functioning 15.17 ±2.91, verbal fluency 9.01 ±3.63, memory 20.17 ±6.11, language 22.74 ±4.96, visuospatial 13.56 ±4.07). Total ACE score, executive functioning, language and visuospatial were significantly worst among women. The results among men and female were respectively: total 83.95 and 76.32 ($p = 0.03$), executive function-

ing 15.69 and 14.46 ($p = 0.02$), verbal fluency 9.43 and 8.44 ($p = 0.15$), memory 20.73 and 19.40 ($p = 0.25$), language 23.66 and 21.51 ($p = 0.02$), visuospatial 14.40 and 12.44 ($p = 0.01$). The results of the ACE test in all domains were significantly worst among patients with an education level lower than diploma ($p < 0.02$). The results among patients with the education level of diploma or higher and patients with education level under diploma were respectively: total 85.91 and 67.81, executive functioning 16.03 and 13.03, verbal fluency 9.98 and 6.60, memory 21.23 and 17.54, language 23.87 and 19.93, visuospatial 14.60 and 11.00. Cognitive impairment of participants was not significantly related to variables such as handedness, smoking and opioid use ($p > 0.01$), although there were significant differences in the size of the compared groups, which reduced the value of the analysis. Regression analysis showed that education level had a significant impact in all domains and the total ACE test, and gender had had a significant impact in executive and memory domains and the total ACE test. In addition, statistical analysis showed a correlation of hemoglobin level with language and visuospatial domains ($p = 0.01$), CRP with verbal domain ($p = 0.01$) and Bili-T with memory domain ($p = 0.03$) (Fig. 1); but no correlations between total result of the ACE test and laboratory findings were seen in statistical evaluation ($p > 0.05$).

Discussion

Increasing cases of neuropsychological involvement with different patterns and severity have been reported in COVID-19 patients (Ellul *et al*. 2020; Varatharaj *et al*. 2020). Most of our knowledge about neurocognitive involvement of SARS-CoV-2 is from studies on patients with the severe form of the disease and after recovery from the initial stage. Here we studied laboratory data of hospitalized patients to see if there is any relation with possible cognitive decline. Studying more than a hundred patients with mild to moderate form of the disease in the acute phase makes this study rather unique.

In this study, cognitive impairment was observed in 63% of patients. Cognitive involvement among COVID-19 patients during hospitalization was first described in Wuhan, China with non-specific encephalopathy (headache, confusion, and disorientation) in 25% (53/214) of patients (Ellul *et al*. 2020). Then higher rates of cognitive involvement from European countries were reported as 69% (of 58 cases) in a French Study (Helms *et al*. 2020) and

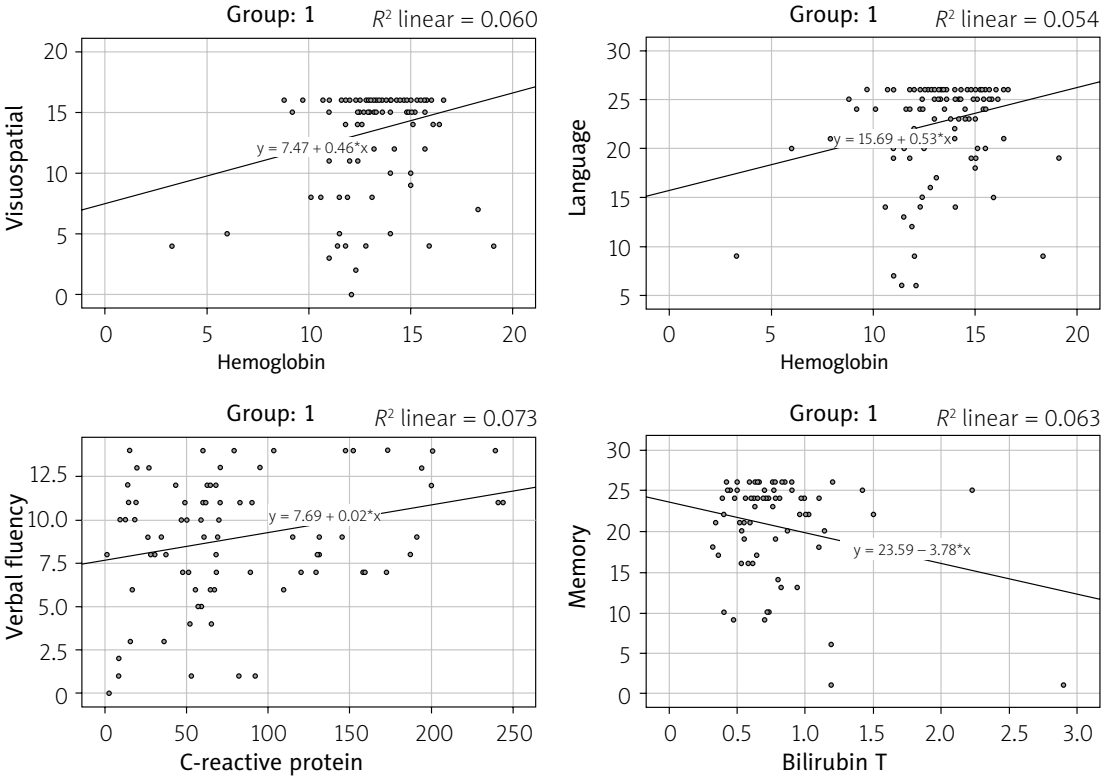

Fig. 1. Statistical analysis showed the correlation of hemoglobin level with language and visuospatial domains, C-reactive protein with verbal domain and bilirubin T with memory domain

31% (of 125 cases) in a UK survey (Varatharaj *et al*. 2020).

Neurocognitive involvement in COVID-19 can occur in different stages of the disease. Here we studied patients in the acute phase of the disease before hospital discharge. Neurological manifestations in COVID-19 often occur during the second week of the disease onset (Mao *et al*. 2020; Ellul *et al*. 2020; Paterson *et al*. 2020; Román *et al*. 2020; Koralnik and Tyler 2020). Matos *et al*. (2021) studied 7 patients with mild/moderate disease and reported neurological symptoms manifesting a median of 16 days after initial COVID-19 symptoms. However, some reports have described delayed neurological manifestations; also there are reports of persistent neurocognitive symptoms in the post-acute phase (Negrini *et al*. 2021; Woo *et al*. 2020; Heneka *et al*. 2020). A study by Raman *et al*. (2021) described impaired cognitive performance after hospital discharge 2-3 months after disease onset. Miskowiak *et al*. (2021) reported cognitive impairment a median of 4 months after hospitalization.

We found verbal fluency to be most affected in COVID-19. Consistently with our study, Matos *et al*. (2021) reported cognitive impairment mainly in verbal fluency (Montreal Cognitive Assessment) and visuospatial skills. Raman *et al*. (2021) studied 58 COVID-19 patients with a control group and observed impaired cognitive performance specifically in the executive and visuospatial domains. Another study by Woo *et al*. (2020) described mild cognitive decline affecting short-term memory, attention and concentration. Miskowiak *et al*. (2021) described cognitive impairment in the post-acute stage of the disease, with verbal learning and executive functions being most affected. Varying patterns and severity of neurocognitive involvement can be seen in COVID-19 patients. The profile of cognitive deficits resulting from COVID-19 is not fully understood. We must be alert to identify manifestations that may occur and thereafter perform more neuropsychological evaluations for patients with COVID-19.

In this study we included hospitalized patients with mild to moderate form of the disease excluding those admitted to an intensive care unit. It should be noted that neurocognitive involvement in COVID-19 is more commonly observed among critically ill patients (Mao *et al*. 2020; Ellul *et al*. 2020; Paterson *et al*. 2020; Román *et al*. 2020; Koralnik and Tyler 2020). A common clinical presentation in COVID-19 patients is acute respiratory distress syndrome (ARDS), which is also associated with cognitive decline (Girard *et al*. 2018; Sasannejad *et al*. 2019). It is reported that about 70% of people with COVID-19 admitted to intensive treatment units require mechanical ventilation and up to 78% of people with ARDS have had cognitive problems a year after discharge and approximately 50% at two years (Ritchie *et al*. 2020). Cognitive deficits can be seen in any COVID-19 patient with mild or severe form of the disease but are more common in severe forms even without an obvious neurological presentation in the acute stage.

Among laboratory data of our patients, the most observed abnormal findings were elevated levels of ESR, CRP, D-dimer, AST, and ALT. COVID-19 is associated with a prothrombotic state and highly elevated levels of D-dimer. Abnormal coagulation factors have been shown to be associated with poor outcome (Tang *et al*. 2020). Experiencing the severe acute respiratory syndrome (SARS) epidemic, it has been revealed that inflammatory cytokines and CRP played an important role in the development of manifestations in SARS (Sheng *et al*. 2005). A recent study of COVID-19 patients suggested that clinical symptoms were associated with inflammatory factor storm and elevated CRP levels (Huang *et al*. 2020). Huang *et al*. (2020) compared ICU patients with non-ICU COVID-19 patients. They reported significantly higher levels of IL-2, IL-7, IL-10, GSCF, IP10, MCP1, MIP1A, and tumor necrosis factor α (TNF-α) among patients admitted to an ICU, and suggested that clinical symptoms were associated with inflammatory factor storm.

In our study, no relation was found between laboratory test results and overall cognitive examination score, but statistical analysis showed a correlation between CRP and verbal fluency ($p = 0.01$), a correlation of hemoglobin level with language and visuospatial domains ($p = 0.01$), and also a correlation of total level of bilirubin with memory ($p = 0.03$). Zhou *et al*. (2020) studied cognitive functions in patients recovered from COVID-19; correlation analysis showed that the reaction time for the Cognitive Performance Test (CPT) was positively correlated with the CRP levels. Miskowiak *et al*. (2021) studied cognitive sequelae of COVID-19 patients 3-4 months after hospital discharge and reported that cognitive impairments were associated with D-dimer levels during acute illness; in their study acute higher maximum D-dimer levels correlated with poorer verbal recall and psychomotor speed. This evidence suggests that

COVID-19 manifestations might be related to inflammatory factors. It should be noted that enzymes involved in inflammatory reactions are found more in limbic and associated brain structures such as the hippocampus and basal ganglia. Accordingly, inflammatory storm in COVID-19 might increase the risk of decline in neurocognitive processes such as memory, attention and emotion (Sartori *et al*. 2012; Raz and Rodrigue 2006).

Exact pathogenic mechanisms responsible for neuropsychological involvement of COVID-19 are not fully understood. It may be due to the inflammatory immune-mediated disease, the direct infection-based effect of the virus on the CNS, or systemic effects of SARS-CoV-2 (Natoli *et al*. 2020). In most cases, however, neuropsychological manifestations may arise from a combination of the above.

Regarding cognitive involvement of SARS-CoV-2, any patient with COVID-19 may experience a deficit whether it is a severe form of the disease or a mild form, as well as in the acute or post-acute stage. It is recommended to pay more attention to neurocognitive involvement in COVID-19 patients, and more evaluations should be performed to detect deficits. There may be a need for interventions targeting specifically neuropsychological aspects in COVID-19 from acute treatment to rehabilitation after recovery from initial symptoms. COVID-19 has challenged all health care providers and will continue to do so for the next few years. We should develop more care for extra-respiratory involvement in the long term and a much more organized healthcare structure to cover the rehabilitation needs of patients.

As a limitation, we could not evaluate patients with the severe form of COVID disease who were admitted to an ICU; hence it is suggested to survey the neuropsychiatric status of these patients. The limited sample size was another limitation; it is recommended to include more patients in future studies. Also, this study was done in a referral hospital, and many patients with complex disorders were referred. It is also recommended that future studies be conducted with a longer follow-up period.

Conclusions

In our study, no relation was found between laboratory test results and overall cognitive examination score, but statistical analysis showed a correlation between CRP and verbal fluency, a correlation of hemoglobin level with language and visuospatial domains, and also a correlation of total level of bilirubin with memory. These relations may suggest that we should follow the neurocognitive features in COVID-19 patients earlier.

Declarations

Study approval statement: This study protocol was reviewed and approved by the Ethics Committee of Tehran University of Medical Sciences, and the reference number is IR.TUMS.VCR.REC.1400.50951.

Consent to publish statement: All the patients who were enrolled in this study signed the consent form, which is available from the corresponding author upon reasonable request. Written informed consent was obtained from the patients for publication of this case series and any accompanying images.

Data availability statement: The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants, but are available from Ahmad Pour-Rashidi [corresponding author] upon reasonable request.

All the patients who were enrolled in this study signed the consent form, which is available from the corresponding author upon reasonable request.

Disclosure

The authors declare no conflict of interest.

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