Neurological symptoms in COVID-19 patients

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ABSTRACT

OBJECTIVES: Our study aimed to investigate neurological symptoms in patients with COVID-19 and contribute to this area of limited knowledge.

BACKGROUND: Increasing evidence shows that neurotropism is a common feature of Coronaviruses (CoVs). Like the other CoVs, SARS-CoV 2 uses angiotensin-converting enzyme 2 (ACE2). The brain is thought to express ACE2 receptors detected on glial cells and neurons. There are also ACE2 receptors in skeletal muscles. Our study aimed to investigate neurological symptoms in patients with COVID-19 and contribute to this area of limited knowledge.

METHODS: A total of 51 patients, presented to hospitalized in our hospital between March 23, 2020 and April 16, 2020 were included in the study. The diagnosis of all patients included in the study was made according to the WHO interim guideline. The patients were divided into two subgroups as mild and severe course according to the severity of the disease.

RESULTS: Neurological symptoms were detected in 16 (31.37 %) patients. Muscle injury was detected in 10 (19.61 %) patients. The most common neurological symptom was headache (n: 9, 17.65 %). When the frequency of all neurological symptoms was compared in those with severe and mild disease, no significant differences were found between the groups. When the frequency of muscular involvement was compared in patients with severe and mild course, no significant differences were found between the groups.

CONCLUSION: The nervous system and skeletal muscle system may be among viral targets. Detection of some neurological findings may be valuable in predicting the course of the disease. Some laboratory values can allow predicting disease severity and neurological symptoms (Tab. 5, Ref. 23). Text in PDF www.elis.sk

KEY WORDS: COVID-19, neurotropism, muscle injury, headache.

Tab. 1. Demographic and clinical features of the patients.

|                | 52.78 | ±20.99 |
|----------------|-------|--------|
| Gender         |       |        |
| Female         | 22    | (43.14)|
| Male           | 29    | (56.86)|
| Severity       |       |        |
| Mild           | 40    | (78.43)|
| Severe         | 11    | (21.57)|
| Muscle injury  | 10    | (19.61)|
| Nervous system symptoms | 16    | (31.37)|
| Headache       | 9     | (17.65)|
| Dizziness      | 7     | (13.73)|
| Impaired consciousness | 4     | (7.84)|
| Hyposmia       | 3     | (5.88)|
| Hypogeusia     | 3     | (5.88)|
| Hypertension   | 17    | (33.33)|
| Diabetes       | 8     | (15.69)|
| Cardio cerebrovascular disease | 4     | (7.84)|
| COPD*          | 5     | (9.80)|
| Malignancy     | 1     | (1.96)|

COPD* – Chronic Obstructive Pulmonary Disease

Introduction

Coronaviruses (CoVs) are large enveloped non-segmented positive RNA viruses. They generally cause respiratory and enteric diseases in humans and animals (1). In many people, CoVs cause mild respiratory disease, but two acute CoVs that had not been previously identified, severe acute respiratory syndrome CoV (SARS-CoV) and the Middle East respiratory syndrome CoV (MERS-CoV), have recently attracted global attention, because they had a lethal potential (2). A new type of CoVs was reported in Wuhan, the capital of China’s Hubei province, in December 2019. It was later revealed that the virus might be contagious among humans. In early January, terms like “new coronavirus” and “Wuhan coronavirus” were widely used. In February, it was named as severe acute respiratory syndrome coronavirus 2 ”(SARS-CoV-2) and then COVID-19 by the world health organization (WHO) (3).
SARS-CoV-2 causes an acute lethal pneumonia such as SARS-CoV and MERS-CoV (2, 4). In many patients with dry cough, dyspnoea and fever, imaging methods showed that there exists a pulmonary involvement dominated by bilateral ground glass density in chest CTs (5). The clinical spectrum of COVID-19 patients ranges from asymptomatic infection to severe pneumonia, which can lead to respiratory failure and death (6).

Most CoVs have a similar viral structure and infection pathway (7). Therefore, infection mechanisms previously described for other CoVs may also be valid for SARS-CoV-2. Increasing evidence shows that neurotropism is a common feature of CoVs (8). The presence of viruses in the cerebrospinal fluid of patients with acute SARS-CoV infection has been demonstrated (3). In addition, in some post-autopsy studies, strong evidence has been obtained on neurological involvement in patients, who had SARS-CoV infection (9). Similar to SARS-CoV, SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) (10). The SARS-CoV-2 uses spike protein S1, which interacts with the host ACE2 receptor, allowing the virus to bind to the cell membrane. The ACE2 binding affinity of SARS-CoV-2 spike protein ectodomain was shown to be 10-20 times higher than that of the SARS-CoV spike protein (11). The brain is considered to express ACE2 receptors detected on glial cells and neurons, making them a potential target of SARS-CoV-2. There are also ACE2 receptors in skeletal muscles (12).

The exact propagation path of SARS-CoV and MERS-CoV to central nervous system (CNS) has not been clearly reported (13). Some experimental studies using transgenic mice have reported that SARS-CoV and MERS-CoV can probably enter the brain through the olfactory nerve when the transmission is intranasal and then rapidly spread to specific areas of the brain, such as the brain stem and thalamus, leading to higher mortality in infected mice with CNS involvement (9, 14). On the other hand, an increasing evidence also shows that CoVs can invade the peripheral nerve terminals first and then have access to CNS in a synapse-related way (15). However, how and to what extent COVID-19 affects the CNS remains unclear. Our study aimed to investigate neurological symptoms in patients with COVID-19 and contribute to the literature in terms of the limited knowledge in this area.

Tab. 2. Comparison of the demographic and clinical features of the patients according to the severity of the disease.

| Gender       | Mild | Severe | Total | p   |
|--------------|------|--------|-------|-----|
| Female       | 18 (45.00) | 4 (36.36) | 22 (43.14) | 0.609 |
| Male         | 22 (55.00) | 7 (63.64) | 29 (56.86) |     |
| Muscle injury| 8 (20.00)  | 2 (18.18) | 10 (19.61) | 0.893 |
| Nervous system symptoms | 10 (25.00) | 6 (54.55) | 16 (31.37) | 0.061 |
| Headache     | 5 (12.50)  | 4 (36.36) | 9 (17.65)  | 0.066 |
| Dizziness    | 5 (12.50)  | 2 (18.18) | 7 (13.73)  | 0.628 |
| Impaired consciousness | 0 (.00)    | 4 (36.36) | 4 (7.84)   | <0.001 |
| Hypoesthesia | 3 (7.50)   | 0 (.00)   | 3 (5.88)   | 0.349 |
| Hypoguesia   | 3 (7.50)   | 0 (.00)   | 3 (5.88)   | 0.349 |
| Hypertension | 11 (27.50) | 6 (54.55) | 17 (33.33) | 0.092 |
| Diabetes     | 4 (10.00)  | 4 (36.36) | 8 (15.69)  | 0.033 |
| Cardiac cerebrovascular disease | 3 (7.50) | 1 (9.09) | 4 (7.84) | 0.862 |
| COPD*        | 3 (7.50) | 2 (18.18) | 5 (9.80) | 0.291 |
| Malignancy   | 0 (.00)   | 1 (9.09)  | 1 (1.96)  | 0.054 |

Chi-square test, COPD* – Chronic Obstructive Pulmonary Disease

Tab. 3. Comparison of laboratory values according to disease severity

| Age (year) | Mild | Severe | Total | p   |
|------------|------|--------|-------|-----|
| 49.50 (18.00–92.00) | 75.00 (53.00–87.00) | 54.00 (18.00–92.00) | <0.001 |
| 13.14 (9.10–16.98) | 12.77 (7.86–17.43) | 13.10 (7.86–17.43) | 0.492 |
| 200.95 (127.70–543.90) | 218.50 (58.46–360.20) | 214.80 (58.46–543.90) | 0.731 |
| 5.72 (2.77–18.90) | 7.60 (4.59–21.73) | 5.92 (2.77–21.73) | 0.078 |
| 3.88 (1.13–12.75) | 5.78 (2.96–19.07) | 4.10 (1.13–19.07) | 0.011 |
| 1.53 (.72–4.20) | 1.01 (.28–2.00) | 1.40 (.28–4.20) | 0.003 |
| 7.55 (5.49–12.90) | 8.01 (5.68–13.64) | 7.66 (5.49–13.64) | 0.384 |
| 1.70 (.16–15.90) | 12.60 (3.44–40.40) | 2.62 (1.6–40.40) | <0.001 |
| .12 (12.27) | .16 (12–1.20) | .12 (12.27) | <0.001 |
| 414.00 (158.00–2580.00) | 3100.00 (845.00–8470.00) | 479.00 (158.00–8470.00) | <0.001 |
| 60.00 (19.00–342.00) | 58.00 (17.00–316.00) | 60.00 (17.00–342.00) | 0.714 |
| 180.00 (142.00–578.00) | 240.00 (168.00–449.00) | 184.00 (142.00–578.00) | 0.038 |
| 21.50 (11.00–45.00) | 23.00 (14.00–56.00) | 22.00 (11.00–56.00) | 0.229 |
| 22.00 (6.00–62.00) | 20.00 (6.00–40.00) | 20.00 (6.00–62.00) | 0.882 |
| 21.00 (10.00–49.00) | 56.00 (23.00–125.00) | 23.00 (10.00–125.00) | <0.001 |
| .74 (.55–1.28) | .78 (.38–5.25) | .74 (.55–5.25) | 0.528 |

Mann–Whitney U Test, HBG – Haemoglobin, PLT – Platelet, WBC – White blood cell count, NEU – Neutrophil, LYM – Lymphocyte, MPV – Mean platelet volume, CRP – C-reactive protein, PCT – Procalcitonin, CK – Creatine kinase, LDH – Lactate dehydrogenase, AST – Aspartate aminotransferase, ALT – Alanine aminotransferase, Cr – Creatinine
| Nervous system symptoms | Total | Mild | Severe | p |
|-------------------------|-------|------|--------|---|
| Age (year)              | 58.00 (19.00 - 87.00) | 51.00 (18.00 - 87.00) | 73.00 (53.00 - 93.00) | 0.144 |
| WBC 10^3/uL             | 5.94 (3.63 - 21.73) | 5.92 (2.77 - 18.90) | 5.56 (3.63 - 18.90) | 0.715 |
| NEU 10^3/uL             | 4.31 (2.17 - 12.75) | 4.09 (2.17 - 12.75) | 8.63 (2.96 - 19.07) | 0.223 |
| MPV fL                  | 7.60 (5.68 - 13.64) | 7.66 (5.49 - 12.90) | 7.72 (5.68 - 10.51) | 0.925 |
| CRP mg/dL               | 4.85 (0.31 - 40.40) | 2.50 (1.68 - 3.30) | 14.30 (7.08 - 32.80) | 0.357 |
| CK U/L                  | 59.50 (17.00 - 229.00) | 60.00 (19.00 - 342.00) | 64.00 (25.00 - 157.00) | 0.243 |
| LDH U/L                 | 187.00 (142.00 - 578.00) | 180.00 (148.00 - 578.00) | 174.50 (142.00 - 578.00) | 0.830 |
| AST U/L                 | 21.50 (12.00 - 49.00) | 23.00 (11.00 - 35.00) | 27.50 (19.00 - 45.00) | 0.189 |
| ALT U/L                 | 16.00 (6.00 - 56.00) | 18.00 (6.00 - 78.00) | 14.50 (6.00 - 35.00) | 0.164 |
| Uremg/dL                | 27.50 (14.00 - 48.00) | 32.80 (14.00 - 62.00) | 35.00 (25.00 - 40.00) | 0.081 |
| CR mg/dL                | 0.86 (0.55 - 1.28) | 0.73 (0.55 - 1.28) | 0.88 (0.58 - 5.25) | 0.638 |

### Results

A total of 51 patients diagnosed with COVID-19 were included in the study. The demographic and clinical features of the patients are summarized in Table 1. The mean age of the participants in the study was 52.78 ± 20.99 and consisted of 22 women (43.14%) and 29 men (56.86%). The lowest patient age was 18, and the highest patient age was 92. When evaluated in terms of comorbid disease features, hypertension was observed as the most common additional disease in all the patients (n: 17, 33.33%). This was followed by diabetes (n: 8, 15.69%), chronic obstructive pulmonary disease (n: 5, 9.80%) cardio-cerebrovascular disease (n: 4, 7.84%) and malignancy (n: 1, 1%, 96).
Muscle injury was detected in 10 (19.61%) patients. The most common neurological symptom was headache (n: 9, 17.65%). This symptom was followed by dizziness (n: 7, 13.73%), impaired consciousness (n: 4, 7.84%), decreased sense of smell (n: 3, 5.88%), and decreased sense of taste (n: 3, 5.88%). When the frequency of all neurological symptoms was compared between the patients with mild and severe disease, no significant difference was observed (p: 0.061). While consciousness affection was more common in patients with severe disease course (p < 0.001), no significant difference was found in relation to the remaining neurological symptoms. When the frequency of muscular injury was compared in the patients with severe and mild course, no significant difference was found between the groups (p: 0.893). Comparison of the demographic and clinical features of the patients according to the severity of the disease is summarized in the Table 2.

When laboratory values were compared between mild and severe disease severity, neutrophil (NEU) (p: 0.011), C-reactive protein (CRP) (p < 0.001), procalcitonin (PCT) (p < 0.001), D-dimer (p < 0.001), lactate dehydrogenase (LDH) (p: 0.038) and blood urea nitrogen (ure) (p < 0.001) were significantly higher, while the value of lymphocyte (LYM) (p: 0.003) was significantly lower. When the patients with and without neurological symptoms were compared, D-dimer (p: 0.048) was found significantly higher in patients with neurological symptoms, while LYM (p: 0.026) levels were found significantly lower. When the patients with and without neurological symptoms in the subgroups of patients, determined according to the severity of the disease, were compared in the terms of laboratory values, there was no significant difference between the values. Laboratory values of the patients with and without neurological symptoms were summarized in the Table 4. Laboratory values were compared between the patients with and without muscle injury. Patients with muscle injury had a significantly higher CK (p < 0.001), LDH (p: 0.006), aspartate transaminase (AST) (p: 0.002) and alanine transaminase (ALT) (p: 0.003) values. Similarly, patients with mild disease severity and muscle injury had a significantly higher CK (p < 0.001), LDH (p: 0.014), AST (p < 0.001) and ALT (p: 0.002) values. Patients with severe disease severity and muscle injury had a significantly higher CK values (p: 0.034). Laboratory values of the patients with and without muscle injury are summarized in the Table 5.

**Discussion**

Coronaviruses can cause multiple systemic infections and effects in various animals (17). In contrast, the number of studies...
involving neurological symptoms in patients with COVID-19 is limited, and the information on this topic is unclear.

In a study conducted in Wuhan and investigating neurological symptoms, it was reported that the most common neurological symptoms in patients were: dizziness and headache. In the study, among other neurological symptoms, taste, and smell disorder, the impaired consciousness and acute cerebrovascular disease (CVD) were found. Epileptic seizures were reported in one patient (18). The results that we found in our study partially overlapped with the aforementioned study. The most common neurological symptom in present study was headache. While changes in smell, taste disorder and impaired of consciousness were observed in our patients, CVD and epileptic attacks were not observed.

Some studies have shown that the patients with a serious spectrum of diseases develop more neurological symptoms (18, 19). In addition, there are also studies, in which potential brainstem respiratory center neuroinvasion is considered to play a role in patients with an acute respiratory failure (20). In our study, consciousness change was observed more frequently in the patients with severe disease course. But no significant correlation was found between the disease spectrum and the development of the other neurological symptoms. This result may also be due to relatively small number of patients with serious disease spectrum in our study. However, it should be kept in mind that neurological symptoms can also be seen in patients with a mild disease course.

How the SARS-CoV-2 affects the CNS is controversial. The movement to the brain through the cribriform plate in the neighbourhood of the olfactory bulbus can be an additional way that allows the virus to reach the brain. Findings such as: altered sense of smell or hyposmia in patients should be investigated in terms of CNS involvement (3). On the other hand, it was reported that loss of sense of smell was found more frequently in patients with mild disease and in ambulatory patients. In a study, it was presented as a hypothesis that viral spread was limited in the nasal epithelium and did not cause pulmonary invasion in patients with a mild course with olfactory dysfunction (21). A decreased sense of smell may be the result of a peripheral effect. It seems that more evidence is needed to think of CNS involvement in patients with hyposmia. In our study, all the patients with a decreased sense of smell were detected in mild cases and pulmonary involvement was not observed in these patients. According to this hypothesis, the presence of olfactory dysfunction may be prognostic in determining the severity of the disease. In addition, people may not tend to identify or care for the loss of sense of smell. This may cause patients with a mild disease or asymptomatic to be overlooked.

Studies showed that COVID-19 patients might have muscle injury (18, 22). In the current study, we found muscle involvement in our patients (17.6 %) in accordance with the previous studies. Patients with muscle symptoms had higher CK and LDH levels than those without muscle symptoms in our study. This affect may be related to the ACE2 receptor found in skeletal muscles (23). On the other hand, it should be kept in mind that significantly elevated pro-inflammatory cytokines in the serum may cause muscle damage, but in our study, muscle injury was also detected in the patients with a mild disease with low inflammatory parameters and frequency of muscular injury was compared in the patients with severe and mild course, no significant difference was found between the groups. This suggests that muscle injury may be independent of the course of the disease. It also shows the importance of laboratory parameters. Mild and overlooked cases can be diagnosed more accurately by using laboratory parameters.

In our study CRP, PCT and NEU levels were found significantly higher in patients with a severe disease course. This may make us think that the systemic inflammatory response plays a role in disease severity. In addition, LYM levels were found to be lower both in the patients with severe disease course and in the patients with neurological symptoms. It may be thought that immune deficiency plays a role in the progression of the disease and the emergence of neurological complications. In addition, D-dimer level of the patients with a severe disease was found significantly higher than in those with mild a disease. Similarly, D-dimer level was found higher in the patients with neurological symptoms compared to those without neurological symptoms. This result reminds the possibility that vascular pathologies may be effective in the emergence of morbidity, mortality and complications of the disease. Further studies focusing on vascular imaging can clarify this issue.

There are some limitations in our study. Our retrospective study is limited to a short sampling period. The number of patients participating in the study was relatively small. Also, as many patients still stayed in the hospital, information on clinical outcomes was not available during the analysis, so it was difficult to assess the impact of these neurological symptoms on the results.

Conclusion

Consequently, COVID-19 may not be limited to only respiratory system involvement. The nervous system and skeletal muscle might also be affected. Detection of some neurological symptoms in COVID-19 may be valuable in predicting the course of the disease. COVID-19 can be missed out by diagnosing other specific neurological diseases in patients with neurological symptoms. Findings obtained from laboratory data in patients may be predictive in terms of disease progression. This may be determinative in deciding, which patients should be followed up closely or to whom an aggressive treatment should be given. Broader-based studies on neurological involvement in the future might shed light on both patient management and how the CNS is affected.

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