

Cerebral Microembolism in Patient with COVID-19

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ABSTRACT

Objective: Coronavirus-2019 (Covid-19) was first observed in December 2019 and recognized as a pandemic by the World Health Organization. Apart from respiratory symptoms, neurological, dermatological, and gastrointestinal symptoms can also occur in humans. Some neurological symptoms may be caused by microembolism. The present study aims to determine the presence of microemboli in patients with Covid-19 using Transcranial Doppler (TCD) ultrasonography and examine its correlation with D-Dimer levels.

Material and Methods: This study involved 20 hospitalized patients diagnosed with Covid-19 using the Polymerase Chain Reaction (PCR) method. D-Dimer results of the patients were recorded and analyzed within two groups (First group: D-Dimer < 1 mg/L, and second group: D-Dimer ≥ 1 mg/L). The middle cerebral arteries were bilaterally examined with TCD to screen for microemboli. Patients were classified into two groups based on the number of MES (first group: 0-3 MES (n=10), second group: ≥ 4 MES).

Results: Cerebral arterial microemboli were observed in patients with Covid-19. The relationship between D-Dimer and emboli was investigated, and the presence of microemboli was found to be statistically significant in both the low D-Dimer value group (p < 0.001) and the high D-Dimer value group (p < 0.003). Furthermore, D-Dimer results were found to be higher in the group with a greater number of microemboli (p < 0.001).

Conclusions: Microemboli were detected in the cerebral arteries of Covid-19 patients, even in the absence of neurological symptoms. Additionally, a positive correlation was observed between high D-Dimer levels and the presence of cerebral microemboli. Therefore, physicians should assess the presence of microemboli in Covid-19 patients and determine appropriate treatment methods accordingly.

Keywords: Covid-19, SARS-Cov-2, Transcranial Doppler, Cerebral Microemboli

INTRODUCTION

Coronavirus (CoV) is an enveloped RNA virus family that is commonly prevalent in society, similar to the common cold. It may cause very mild flu-like symptoms, as well as it can cause to be varied clinical manifestations which reflect severe respiratory failures such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) (1-4). In addition to the respiratory system, neurological, dermatological and gastrointestinal system symptoms can also be seen in humans (5-9).

By the end of 2019, it was observed pneumonia cases which reason is not completely determined in Wuhan, China. At the beginning of 2020, a newly-detected coronavirus type (2019-nCoV) was identified as the cause of this circumstance, and the disease that developed due to this virus was named COVID-19 (10). The disease spread all over the world in a short time and World Health Organization declared a pandemic in March 2020. The number of deaths allied to disease has also increased in parallel. According to the first data obtained from China, it was reported that deaths were generally seen in elder age or immunosuppressive individuals or people with concomitant systemic diseases such as hypertension, diabetes, cardiovascular disease, and cancer (11, 12).

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However, as the number of cases increased and the disease spread around the world, young individuals without any disease were also lost due to COVID-19. Symptoms occur in patients after an incubation period of approximately 5 days (13). Fever, respiratory failure, and fatigue are the most commonly observed symptoms in Covid-19. However, due to the global increase in the number of cases, neurological symptoms such as headache, seizure, stroke, smell-taste disturbance, neuralgias, and changes in consciousness have also been reported (14, 15). The exact pathological mechanisms of neurological involvements such as stroke, systemic thrombus, and headache in these patients is still unknown. Coagulopathies have been identified in patients with Covid-19, and it has been suggested that these coagulation abnormalities contribute to the poor prognosis of the disease. Also, it has been shown the significant mortality decreases with the use of heparin (16).

While thromboses stroll in the cerebral arteries, they produce a sound, and these micro-embolic signals can be detected in real-time using Transcranial Doppler (TCD) Ultrasonography (17-19). TCD is a noninvasive functional tool to assess cerebral hemodynamics Cerebral microemboli is described in several diseases by using TCD (20). For this reason, the present study aims to investigate:

1. The presence of microemboli in the central nervous system arterial system using Transcranial Doppler (TCD) in patients with Covid-19.
2. Relation between D-Dimer levels and microemboli

MATERIAL and METHODS

This study was conducted on 20 patients who hospitalized and diagnosed with Covid-19 confirmed by positive reverse transcriptase polymerase chain reaction assay (RT-PCR) in nasopharyngeal swab. Patients had no neurological complaints. Participants who were taking anticoagulants and antiplatelet medications, had a history of previous stroke, myocardial infarction, rheumatologic diseases, malignancy, or coagulation disorders were excluded from the study. Demographic data of patients were recorded. TCD tests were performed on 20 patients, starting with a random hospitalized patient. TCD studies were performed just after the hospitalization before any treatment for Covid-19. The first D-Dimer results of patients in due course of hospital admission were used for this study. D-Dimer results of patients were recorded as well and analyzed within 2 groups (First group D-Dimer <1 mg/L (n:13) and second group D-Dimer \geq 1 mg/L (n:7)).

DWL Multi-Dop T tool and QL software 2.8 were used for TCD detection. The Middle Cerebral Arteries (MCA) were detected at an average depth of 48-60 mm through the bilateral temporal bone window by means of a 2 Mhz probe. To reduce motion artifacts, both probes were fixed to the head with a helmet, and Microembolic Signals (MES) were recorded with 30 minutes duration. MCA records were made at two different depths. The cut-off value was determined as a 9db for separating artifacts and MES record (21). Patients were evaluated within 2 groups according to the numbers of MES (first group 0-3 MES (n:10), second group \geq 4 MES (n:10)).

The criteria for identification and detection of microemboli were those of the International Consensus Group on Microembolism Detection: (1) characteristic acoustic qualities, (2) short duration (<300 ms), (3) random appearance in the cardiac cycle, (4) unidirectional signal, and (5) an intensity increase at least 9 dB above background noise (19). To distinguish microembolic signals (MES) from artifacts, signals generated simultaneously from both sides or obtained from different depths of the same artery were considered as artifacts. The recorded signals were evaluated by two neurologists, and signals that reached a consensus were identified as MES. Before the study, all patients were informed about the study and written consent forms were taken. This study was approved by the Local Ethic Committee (Protocol No: 25.08.2020-316).

Statistical Analyses

The data were analyzed with SPSS 26 for Windows. After visual and statistical normal range criteria were tested for suitability; parametric tests were performed. Chi square tests were performed to evaluate the relationship between categorical variables, and t- test to evaluate the differences of the median values of two groups. The data were evaluated as mean and standard deviation. The data in each group were evaluated with Pearson's correlation and $p < 0.05$ is accepted as statistically significant.

RESULTS

The study was conducted on 20 patients (13 male+7 females) with Covid-19 diagnosis. The diagnosis was confirmed with PCR modality. The lowest age was 38 and the highest age was 78. The mean age of the patients was 52.75 ± 11.25 . Patients were evaluated within 2 groups according to the numbers of MES (first group 0-3 MES (n:10), second group \geq 4 MES (n:10). D-Dimer results of patients were recorded as well and analyzed within 2 groups (First group D-Dimer <1 mg/L (n:13) and second group D-Dimer \geq 1 mg/L (n:7)). The relationship between D-Dimer and emboli was investigated, and the presence of microemboli was found to be statistically significant regardless of the D-Dimer levels. On the other hand, D-Dimer results were found to be higher in the group with more microemboli ($p < 0.001$) (Table 1).

Table 1: Common Data and Findings

		MES (Microembolic Signals)
Male	n:13	
Female	n:7	
Age (Min, Max)	(Mean)	
38, 78	52.75 \pm 11.25	
0-3 MES	n:10	
\geq 4 MES	n:10	
D-Dimer <1 mg/L	n:13	
D-Dimer \geq 1 mg/L	n:7	$p < 0.001$

DISCUSSION

In this study the presence of microemboli was investigated in the bilateral MCA via TCD in patients diagnosed with Covid-19, and the relationship between microemboli and D-Dimer levels was evaluated. As a result, cerebral arterial microemboli in patients with Covid-19 and a positive correlation between the intensity of microemboli and higher D-Dimer levels were observed.

The cause of hypercoagulability in Covid-19 disease is not fully known. It may develop in endothelial cells as a result of being infected by the SARS-CoV-2 virus or being affected by cytokines such as IL-6 (22). Immobilization is another facilitative factor for hypercoagulability in these patients. In addition, high levels of factor VIII and fibrinogen in the blood of patients with Covid 19 can also cause coagulation disorders (23, 24). D-Dimer values were detected to be high in patients with Covid 19 and this height was related to the disease's severity (25, 26). Low molecular weight heparin therapy has also been found to be effective in survival, especially in patients with high D-Dimer levels (27). In addition to its anticoagulant effect, the anti-inflammatory effect of heparin also plays a role in this success.

In one study conducted by Klok et al., 25 pulmonary emboli cases were reported in a series of 184 patients with Covid 19 (16). In the same study, venous thromboembolism (VTE) was detected in 27%, while arterial thromboembolism was observed in 3.7%. In another study, carried out by Helms et al., it was compiled, 150 intensive care patients. As a result of the study, the VTE in 64 patients and arterial thromboembolism in 4 patients (two cerebral and two peripheral) were reported in total (26). In addition, Logidigani et al. stated 9 ischemic stroke cases in 388 patients in their study (28).

22 pulmonary emboli in 107 intensive care patients were reported in another study (29). Also, Llitjos et al. evaluated Covid-19 patients in intensive care in their study and performed the lower extremity USG on the patients. According to the study results, VTE was observed in 18 of 26 patients, 10 of which were bilateral (30).

A limited number of autopsy studies have shown a microvascular thrombosis in the lungs of patients with COVID-19 (22, 31). In one study Oxley et al., have reported 5 cases of ischemic stroke in a 2-week period under the age of 50 (32). Cases of cerebral and peripheral arterial thromboembolism have also been reported in different studies (32-37). In another TCD ultrasonography study, Batra et al confirmed cerebral microemboli in three of six Covid-19 patients (38).

CONCLUSION

As a result of our study, it was detected microemboli in the cerebral arteries in Covid-19 patients, even if they did not have any neurological complaints. Also, a positive correlation was observed between the high D-Dimer result and the presence of cerebral microemboli. No embolic event was observed in these patients during their hospitalization. After the diagnosis of the patients in our center, LMWH treatment was started for all patients in accordance with the recommendation of the Ministry of Health. As a result, no

clinically embolic event (Systemic thrombosis or cerebral stroke) occurred in our patients.

This study has several limitations. One of the limitations of our study is that we did not evaluate the presence and intensity of emboli during the follow-up of these patients. Also, all of our patients' symptoms were mild or moderate. At the time of the study, all patients diagnosed with Covid-19 were hospitalized, even if they had very mild symptoms. None of our patients were in intensive care units or needed oxygen support. In future, the presence and intensity of emboli during the follow-ups the correlation of microemboli and prognosis should be investigated in a multicenter study.

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Ethical approval: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions.

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