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Transcranial Doppler Ultrasound Evidence of Active Cerebral Embolization in COVID-19

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Objective: To report six consecutive patients with confirmed coronavirus disease-2019 (COVID-19) who underwent Transcranial Doppler (TCD) ultrasonography evaluation for cerebral microemboli in the setting of suspected or confirmed acute ischemic stroke. *Methods:* Patient data were obtained from medical records from Northwestern Memorial Hospital, Chicago, IL between May and June 2020. All patients with confirmed COVID-19 who underwent clinical TCD ultrasonography for microemboli detection were included. *Results:* A total of eight TCD studies were performed in six patients with COVID-19 (4 men and 2 women, median age 65±5), four with confirmed ischemic stroke and two with refractory encephalopathy. Microemboli were detected in three male patients, two patients had suffered a confirmed ischemic stroke and one who developed prolonged encephalopathy. Microemboli of varying intensity were identified in multiple vascular territories in two patients, and microemboli persisted despite therapeutic anticoagulation in a third patient. Of the three patients without evidence of microemboli on TCD ultrasonography, two patients had suffered a confirmed ischemic stroke, while one remained with refractory encephalopathy. *Conclusions:* TCD ultrasonography for microemboli detection identified three patients with confirmed COVID-19 with evidence of cerebral arterial microemboli, including one who was therapeutically anticoagulated. TCD ultrasonography provides a non-invasive method for evaluating cerebral microemboli in patients with COVID-19 and may be useful in assessing response to treatment in cases with suspected or confirmed disorders of hypercoagulability. Further studies investigating the prevalence of cerebral microemboli and associated risk factors are needed to characterize their pathogenic mechanism and guide therapeutic interventions in hospitalized COVID-19 patients.
Key Words: Cerebrovascular disease/Stroke—Embolism—Ultrasound—Viral infections—COVID-19

Introduction

As of October 5th, 2020, there have been over 35 million confirmed cases of severe acute respiratory syndrome-coronavirus type 2 (SARS-CoV-2) infection resulting in over 1 million deaths worldwide. While symptomatic patients with coronavirus disease 2019 (COVID-19) commonly present with respiratory symptoms, others may develop gastrointestinal disturbance, cardiac dysfunction, as well as hypercoagulability with thromboembolic events, including ischemic stroke.[1−7]

Transcranial Doppler (TCD) ultrasonography provides a noninvasive functional assessment of blood flow characteristics and cerebrovascular hemodynamics within the basal arteries of the brain.[8,9] Circulating microemboli within the cerebral arteries can be detected in real-time using TCD ultrasound waves that are backscattered from the surface of emboli and manifest as high-intensity transient signals (HITS) within the doppler spectrum.[8−10] Prior studies demonstrate that the presence of cerebral microemboli is predictive of future ipsilateral stroke and transient ischemic attack in both patients with symptomatic and asymptomatic carotid stenosis.[10−13] TCD microemboli have also been described in patients with myocardial ischemia, atrial fibrillation, mechanical cardiac valves, antiphospholipid antibody syndrome, neuropsychiatric systemic lupus erythematosus, and cerebral and systemic vasculitis.[9,10,14] We describe a series of consecutive TCD microemboli detection studies performed over a two week period in six patients hospitalized with COVID-19. Studies were performed as part of the evaluation for either acute ischemic stroke or suspected ischemic stroke in the setting of persistent encephalopathy of unknown etiology. This series demonstrates evidence of circulating microemboli in COVID-19 patients and may provide early insights into those COVID-19 patients for whom TCD microemboli detection may be of clinical utility.

Methods

Beginning in late May 2020, the clinical neurosonology laboratory at Northwestern Memorial Hospital, Chicago, IL dedicated a DWL Doppler-BoxX TCD machine (Compumedics; Singen, Germany) to use in patients infected with SARS-CoV-2 for evaluation of ischemic stroke. TCD microemboli detection studies are performed routinely within our hospital as standard evaluation for ischemic stroke. All COVID-19 TCD studies were performed by a single operator experienced in equipment decontamination and personal protective equipment procedures (EML). After each TCD study, the equipment was thoroughly decontaminated with hospital-grade disinfecting solutions, covered with an impermeable plastic barrier, stored in a locked space in the neurosonology laboratory, and only used for confirmed COVID-19 patients. This approach is consistent with recent guidelines by the European Society of Neurosonology and Cerebral Hemodynamics (ESNCH).[15]

The diagnosis of COVID-19 was confirmed by positive reverse transcriptase polymerase chain reaction assay (RT-PCR) in nasopharyngeal swab. TCD microemboli detection studies were performed on any COVID-19 patient with clinical suspicion for stroke, transient ischemic attack, or persistent encephalopathy of unknown etiology. In the case of persistent encephalopathy, patients' critically ill status precluded advanced structural neuroimaging to assess for ischemic lesions at the time of TCD study request. Of relevance, autopsy series in COVID-19 patients have suggested that those with cerebral microemboli are more likely to demonstrate small, multi-focal infarcts than large territorial infarcts;[3] such cerebral infarcts might not clearly manifest with typical stroke syndromes on clinical exam in critically ill patients. Each clinical TCD study was obtained at the request of the consulting vascular neurology or neurocritical care attending physician. The consulting attending physician requested the basal arteries to be studied based on assessment of the available clinical data. When a systemic source of embolism is of concern, our laboratory generally recommends middle cerebral artery (MCA) insonation as the initial study; however, alternative arteries may be insonated initially depending on the consulting attending physicians' clinical assessment and repeat assessment of the same or alternative arteries may be performed at the attending physicians' request. The selected basal arteries of the brain were monitored through the temporal acoustic window with the patient supine and resting quietly using a headset and 2 MHz monitoring ultrasound probes with 8 mm sample volumes.[10,16] Monitoring was performed for 45−65 min, depending on patient comfort and tolerance.[10,16,17] The basal arteries were identified by the combination of probe orientation, insonation depth, and direction of blood flow.[9] Microemboli were identified during the study acquisition followed by audio and visual confirmation using the recorded study (by EML). Study findings were confirmed by two additional experienced neurosonographers (FAS, KL). A detection threshold 9 decibels above baseline was used to identify microemboli.[16,17] Microemboli are characterized by short lasting (<0.01−0.03 s), unidirectional intensity increases within the Doppler spectrum that occur randomly in the cardiac cycle and produce a "clicking" sound as they pass through the sample volume.[10,16,17] Patients' clinical history, laboratory, and imaging data was extracted by medical chart review, according to an institutional review board approved protocol and as previously described (NU IRB #: STU00212627).[18] The clinical course and neuroimaging studies for patients with and without microemboli detected are summarized individually.

Results

Over a two-week period, six patients hospitalized with COVID-19 underwent eight TCD microemboli detection studies. Microemboli were detected in three patients. Table 1 summarizes the patient demographics, indication for emboli detection study, emboli detection study result, cardiac and angiographic evaluation, and laboratory markers of systemic inflammation and COVID-19 disease severity at the time of TCD acquisition. Fig. 1 demonstrates the pertinent radiographic findings from those patients with microemboli detected. Brief clinical course descriptions are provided below with further detailed descriptions provided in Supplemental Material—Case Descriptions.

Patients with Microemboli Detected

Case 1: A 66-year-old male with history of asthma and hypertension was hospitalized after presenting with fevers, chills, nausea, vomiting, and diarrhea. He had similar symptoms 6 weeks prior to presentation, when a nasopharyngeal swab RT-PCR was positive for SARS-CoV-2, but had no neurologic complaint at that time. On hospital day three, he developed new onset atrial fibrillation and subsequently developed acute left hemiparesis with NIH stroke scale of 15. CT brain (Fig. 1A) and CT angiography head demonstrated a substantial right middle cerebral artery (MCA) territory hypodensity with proximal right MCA occlusion. The patient was not a candidate for thrombolysis given time from confirmed last known well; however, CT perfusion demonstrated a cerebral blood flow to transit time ratio favorable for treatment with mechanical thrombectomy. Despite multiple passes with a stent retriever thrombectomy device with aspiration catheter and eptifibatide infusion, the MCA occlusion could not be recanalized (Fig. 1B). Of note, only the right cerebral circulation was selectively catheterized during angiography. Six hours after thrombectomy attempt, a TCD microemboli study was performed in the intensive care unit with monitoring of the right proximal MCA, right anterior cerebral artery (ACA), and left proximal MCA. Over fifty microemboli, ranging in intensity from 10-30 decibels, were detected during 65 min of monitoring, with multiple emboli detected per monitored artery (Supplemental Video and Supplemental Figure, >45 microemboli per hour).

Case 2: A 71-year-old male with history of asthma, type 2 diabetes mellitus, hyperlipidemia, and hypertension presented to an outside institution with chest pain, abdominal pain, dyspnea, and diarrhea and was diagnosed with SARS-CoV-2 infection by nasopharyngeal swab RT-PCR. He had been experiencing symptoms for nearly two weeks prior to hospitalization. He was admitted for hypoxia, requiring 6L nasal canula oxygen, subsequently necessitating intubation. Therapeutic anticoagulation with heparin infusion was briefly started in response to an increased blood D-dimer concentration of 2200 ng/mL, and subsequently transitioned to enoxaparin twice daily prophylaxis dosing. He was transferred to our institution where he required three days of paralysis and intermittent prone positioning for refractory hypoxemia, after which the inhaled fraction of oxygen and positive end expiratory pressure were able to be downtitrated. His sedative infusions were weaned and systemic metabolic derangements demonstrated improvement; however, the patient remained comatose with a Glasgow Coma Scale of three and intact brainstem reflexes. At that point, TCD microemboli detection was requested as part of a refractory encephalopathy evaluation. Bilateral MCAs were insonated for 45 min and a 14-decibel right MCA embolus was detected (Fig. 1D). In addition, innumerable small microembolic signals of 9 to 10 decibels were detected in the bilateral MCAs (>50 microemboli per hour). Therapeutic heparin infusion was initiated in response to the TCD findings. After 96 h of therapeutic anticoagulation, a repeat 60 min TCD study of the bilateral MCAs demonstrated no microembolic signals. An MRI of the brain, four days after the initial TCD study, demonstrated multiple small diffusion weighted and apparent diffusion coefficient map lesions consistent with subacute punctate infarcts (Fig. 1E, 1F).

Case 3: A 64-year-old male with history of hypertension, type 2 diabetes mellitus, hyperlipidemia, chronic kidney disease, and ischemic stroke, presented to our emergency department with acute onset of dizziness, nausea and vomiting, and confusion. Eleven days prior, the patient had presented to our hospital with complaints of nausea, diarrhea, dry cough, mild confusion, and fever, testing positive for SARS-CoV-2 by nasopharyngeal swab RT-PCR. At that time, he was admitted to the COVID-19 medical floor and a CT scan of the head demonstrated the known chronic infarct in the left posterior cerebral artery (PCA) territory (Fig. 1G) but no acute findings. After eight days, his symptoms resolved and he was discharged home. The day after discharge, he represented with dizziness, emesis, and confusion and, while in the emergency room, developed acute dysarthria, right facial droop, and right arm pronator drift along with acute left cranial nerve three and six palsy and ataxia (NIH stroke scale of 13). The patient was not a candidate for thrombolysis due to time from last known well, but underwent a rapid MRI of the brain with MR angiography head/neck which revealed acute infarcts in the left occipital lobe, pons and cerebellum (Fig. 1H), but no target occlusion for mechanical thrombectomy. A 60 min TCD microemboli study of the bilateral MCAs was performed within 12 h of hospital admission and revealed no evidence of emboli. Subsequently, an echocardiogram demonstrated a dilated left ventricle with 35% ejection fraction and multiple akinetic and severely hypokinetic segments. In response to these findings, therapeutic anticoagulation with unfractionated heparin was initiated. A second 45 min TCD microemboli

Table 1. *Patient past medical history, COVID-19 symptoms, TCD results, cardiac and angiographic evaluation, and serum laboratory studies.*

Case	Age (years), Sex	Past Medical History, Pre-morbid Vascular Risk Factors	Presenting COVID-19 Symptoms	Hospital Day TCD Study Obtained	TCD indication	Vessels Insonated, number of HITs	Oxygen-ation Status at the Time of First TCD	Cardiac Rhythm and Echocardio-graphic Evaluation	Angiographic Findings of the Head, Neck, and Chest	Laboratory Studies the Day of TCD acquisition			
										WBC (1000/μL)	CRP (mg/dL)	D-Dimer (ng/mL)	Ferritin (ng/mL)
1	66, Male	Asthma, HTN	Fever, chills, nausea, vomiting, diarrhea	4	Stroke	Right proximal MCA and ACA, Left proximal MCA; >50 bilaterally distributed 10−30 db HITS in 65 minutes	Intubated, FiO2 50%, PaO2 103 mmHg	*Rhythm:* admission normal sinus, hospital day 3 new onset afib *TTE (day 3):* previously unknown LVEF 28%, LV dilation, no shunt, no thrombus; new onset afib *TTE (day 5):* LVEF 19%, severe RV systolic dysfunction, no shunt, no thrombus	*CT and conventional angio (day 4):* right M1 MCA occlusion, non-calcified athero with <10% stenosis of bilateral carotid bulbs, normal aortic arch	27.0	36.2	613	1946.4
2	71, Male	Asthma, HTN, DM2, HLD	Chest and abdominal pain, dyspnea, diarrhea	16, 20	Refractory encephalo-pathy	Bilateral MCA; 1st TCD: 14 db right MCA HIT, numerous small bilateral 9−10 db HITS; 2nd TCD: no HITs	Intubated, FiO2 40%, PaO2 98 mmHg	*Rhythm:* sinus, no afib, occasional PVCs *TTE (day 18):* 65% LVEF, grade 1 diastolic dysfunction, no shunt, no thrombus	*MR angio head and neck (day 20):* no intracranial athero, <25% stenosis of left carotid bulb, no stenosis right carotid *CT chest (day 23):* mild thoracic and no aortic arch athero	1st TCD: 8.2 2nd TCD: 7.4	1st TCD: 28.5 2nd TCD: 11.2	1st TCD: 3526 2nd TCD: 4173	1st TCD: NA 2nd TCD: 1249.1
3	64, Male	HTN, DM2, HLD, chronic kidney disease, stroke	Fever, nausea, diarrhea, dry cough, confusion	1, 3	Stroke	1st TCD: Bilateral MCA, no HITS; 2nd TCD: Bilateral PCA, 24 dB right PCA HIT	Room Air, FiO2 21%, oxygen saturation 95%	*Rhythm:* sinus, no afib, rare PVCs *TTE (day 2):* LVEF 35%, LV dilated without hypertrophy, akinetic and hypokinetic regions, no shunt, no thrombus	*MR angio brain and neck (day 1), CT angio head and neck (day 11):* no aortic abnormality, focal 50% narrowing of left ICA, no narrowing of right common or internal carotid, moderate to severe athero of left vertebral artery origin and intracranial segment, right PCA originates from the right ICA and is without athero	1st TCD: 10.7 2nd TCD: 10.2	1st TCD: 2.8 2nd TCD: 5.9	1st TCD: 5570 2nd TCD: 852	1st TCD: 720.6 2nd TCD: NA
4	59, Female	ESRD, HIV, HTN, DM2, Jehovah's Witness	Fever, nausea, vomiting, diarrhea, fatigue	7	Stroke	Bilateral MCA, no HITs	Room Air, FiO2 21%, oxygen saturation 97%	*Rhythm:* sinus, no afib *TTE (day 7, after TCD):* LVEF 60%, grade 2 diastolic dysfunction, micro-cavitations suggesting small PFO, no shunt, no thrombus	*CT angio head and neck (day 6):* mild aortic arch calcified athero, mild to moderate calcified athero of intracranial vertebral arteries, moderate calcified athero of the bilateral intracranial ICAs	5.1	18.7	480	6191.8
5	58, Male	DM2	Nausea, vomiting, light-headedness, dizziness, fatigue, probable acute stroke	1	Stroke	Bilateral MCA, no HITs	Room Air, FiO2 21%, oxygen saturation 97%	*Rhythm:* sinus, no afib *TTE (day 2):* 44% LVEF and mild global hypokinesis, no shunt, no thrombus	*CT angio head and neck (day 1):* severe stenosis proximal right PCA with distal occlusion, athero of bilateral carotid bifurcations but <50% stenosis	5.2	<0.5	NA	136.5
6	68, Female	HTN, DM2	Fevers, fatigue, cough, dyspnea	14	Refractory encephalo-pathy	Bilateral MCA, no HITs	Intubated, FiO2 55%, PaO2 61 mmHg	*Rhythm:* sinus, no afib, rare PVCs *TTE (day 13):* 64% LVEF, no shunt, no thrombus	Patient never able to medically tolerate transport for angiographic imaging	14.6	16.9	2510	129.2

TCD= transcranial doppler, HIT = High-intensity transient signal, WBC = white blood count, CRP = C-reactive protein, HTN = hypertension, MCA = middle cerebral artery, ACA = anterior cerebral artery, db= decibel, FiO2 = inhalation fraction of oxygen, PaO2 = arterial partial pressure of oxygen, afib = atrial fibrillation, TTE = transthoracic echocardiogram, LVEF = left ventricular ejection fraction, LV = left ventricle, RV= right ventricle, CT = computed tomography, angio = angiography, athero = atherosclerosis, DM2 = type 2 diabetes mellitus, HLD = hyperlipidemia, PVC = premature ventricular contraction, MR = magnetic resonance, ICA =internal carotid artery NA = not available, ESRD = end-stage renal disease
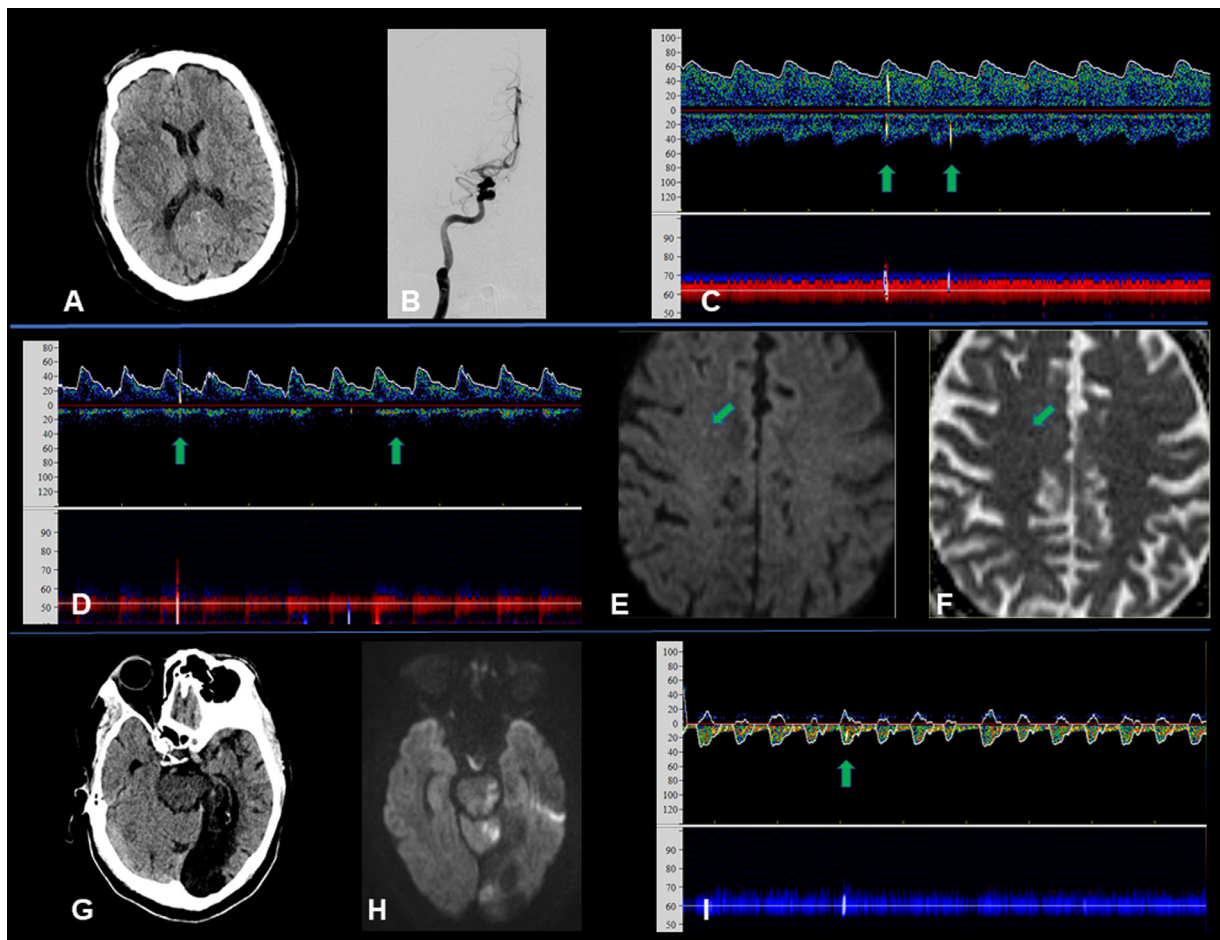
Fig. 1. *Neuroimaging results of patients with cerebral microemboli detected. A.) Case 1. CT brain demonstrating right middle cerebral artery territory hypodensity at the time of acute stroke identification. B.) Case 1. Conventional cerebral angiogram demonstrating the inability to recanalize the right middle cerebral artery occlusion despite multiple stent retriever passes with concurrent eptifibatide infusion. C.) Case 1. TCD doppler waveform demonstrating multiple microembolic signals (17-28 decibels) in the right middle cerebral and anterior cerebral arteries. D.) Case 2. TCD doppler waveform demonstrating a 14-decibel right middle cerebral artery microembolus as well as one of the numerous small 9−10 decibel microemboli that occurred throughout the recording and subsequently resolved after initiation of heparin infusion. E.) Case 2. Diffusion weighted MRI brain demonstrating punctate subacute infarcts in the right hemispheric white matter. F.) Case 2. Corresponding apparent diffusion coefficient map MRI brain confirming punctate subacute infarcts in the right hemispheric white matter. G.) Case 3. CT brain acquired during the patient's first hospitalization for COVID-19 demonstrating the patient's known chronic infarct in the left posterior cerebral artery territory. H.) Case 3. Diffusion weighted MRI brain demonstrating acute infarcts in the left occipital lobe, pons and cerebellum. I.) Case 3. TCD doppler waveform demonstrating 24-decibel right posterior cerebral artery microembolus.*

study of the bilateral PCAs (left PCA originating from the basilar artery, right PCA originating from the right internal carotid artery) was performed 36 h after heparin initiation, while the patient was therapeutically anticoagulated, and demonstrated a 24-decibel right PCA microembolus (Fig. 1I, approximately 1 microembolus per hour).

Patients without Microemboli Detected

More detailed description of these patients may be found in the Supplemental Material—Case Descriptions

Case 4: A 59-year-old female with end-stage renal disease on dialysis, HIV on antiretroviral therapy, hypertension, and type 2 diabetes mellitus presented to our emergency department for 10 days of fevers, nausea and vomiting, diarrhea, and fatigue. Nasal swab was positive

for SARS-CoV-2 and she was admitted to the COVID-19 medical floor. On hospital day 4, the patient developed acute altered mental status. The patient regarded the examiner and moved her extremities purposefully but was unable to follow commands and produced only incoherent verbalization. Continuous electroencephalography demonstrated no seizures or epileptiform discharges but was consistent with moderate global encephalopathy. Lumbar puncture demonstrated a normal profile with 1 white blood cell per µL and protein of 40 mg/dL. MRI brain demonstrated numerous punctate acute infarcts throughout the bilateral supratentorial and infratentorial white matter. A 60 min TCD microemboli detection study of the bilateral MCAs demonstrated no microemboli. A definitive stroke etiology was not determined though the consulting neurovascular attending

physician suspected hypercoagulability in the setting of COVID-19 compounding underlying vascular risk factors and sepsis.

Case 5: A 58-year-old male with history of type 2 diabetes mellitus presented to our emergency department after an outpatient MRI brain demonstrated a subacute right PCA territory infarct. Eighteen days prior to obtaining the MRI, the patient had awoken with nausea, vomiting, lightheadedness, and dizziness as well as a non-specific visual complaints and nasal swab at that time was positive for SARS-CoV-2. At hospital admission, the patient's neurologic exam was only remarkable for a left homonymous hemianopsia. A 65 min TCD microemboli study was performed on bilateral MCAs because adequate signals of the bilateral PCAs could not be maintained and the patient's symptomatic right PCA originated from the anterior cerebral circulation; the TCD study demonstrated no microemboli. The consulting neurovascular attending physician suspected embolic source of unknown etiology, possibly with a contribution from COVID-19.

Case 6: A 68-year-old female with history of hypertension and type 2 diabetes mellitus presented to our emergency department for six days of fevers, fatigue, and cough and one day of dyspnea after a nasal swab performed at an urgent care was positive for SARS-CoV-2. In the emergency department, the patient was afebrile but developed refractory hypoxemia, requiring intubation. The patient required paralysis and intermittent prone positioning for refractory hypoxemia. On the fourteenth hospital day, a TCD microemboli detection study was requested because of persistent coma with Glasgow Coma Scale score of 3 and intact brain stem reflexes despite weaning sedative infusions. A 65-minute TCD study of the bilateral MCAs was performed and demonstrated no microemboli. Before the patient could receive additional neurologic imaging, she developed worsening septic shock and hypoxemia requiring re-initiation of prone positioning. A specific etiology of the encephalopathy was not determined though some component of septic encephalopathy was suspected.

Discussion

In this report, TCD ultrasonography provides direct evidence of microemboli circulating in the cerebral arteries of three of six COVID-19 patients with suspected or confirmed ischemic stroke. Although the number of patients studied was small, this report demonstrates that cerebral microemboli may occur in the absence of severe pulmonary manifestations of COVID-19 (patient 3). Furthermore, microemboli may be detected in critically ill patients with COVID-19 with persistent encephalopathy who did not initially present with neurologic symptoms (patient 2). A causal role for cerebral microemboli in the development of encephalopathy is unresolved, though cerebral microembolism has been hypothesized to contribute to encephalopathy and cognitive dysfunction after surgeries where high rates of microemboli are observed, such as cardiac surgery involving cardiopulmonary bypass.[19,20] Cerebral microemboli have also been associated with a variety of neuropsychiatric manifestations of systemic lupus erythematosus.[10,14]

In addition, case 2 suggests that it may be possible to eliminate cerebral microemboli with therapeutic anticoagulation, but case 3 indicates that cerebral emboli may occur in COVID-19 patients, even while therapeutically anticoagulated. This is consistent with previous literature in patients with symptomatic carotid artery stenosis in whom combination therapy with aspirin and clopidogrel significantly reduced but did not completely eliminate cerebral microemboli after seven days of therapy compared to aspirin alone.[21]

Identification of microemboli in three of six patients studied over a two-week period suggests that cerebral microemboli may not be uncommon in patients with COVID-19 who develop neurologic symptoms. However, our study consisted of patients in whom a neurologic consultation was obtained and the consulting neurologist requested a TCD microemboli detection study; further investigation is required to determine the prevalence of cerebral microemboli in the broader population of hospitalized patients with COVID-19. We also considered a potential relationship between circulating cerebral microemboli and the systemic inflammatory and coagulation markers CRP, ferritin, and D-dimer, which are markers that have been used widely in COVID-19 evaluation.[5,6] While each of these markers was elevated in most of our patients at the time of the TCD study, there was considerable overlap in the range of these markers observed in patients with and without microemboli detected. Additionally, the timing of TCD evaluation from initial symptom onset, and symptom severity once hospitalized varied significantly among this small sample size, which may influence the relationship to measured inflammatory markers. Further research will be required to determine if there are inflammatory and coagulation markers that are useful in predicting those patients at highest risk for circulating cerebral microemboli and subsequent neurologic sequelae.

Numerous potential mechanisms for emboli formation have been described in COVID-19. A recent autopsy series suggested evidence of hypercoagulability as well as endotheliitis and endothelial dysfunction with microthrombi observed in multiple organ systems, including the brain.[3] Acute cardiac injury, heart failure, and arrhythmias have also been observed in COVID-19, with evidence of cardiac dysfunction in up to 60% of severe COVID-19 cases.[5] While TCD can detect circulating cerebral microemboli, the technique is not able to determine the mechanism by which the emboli have formed. However, the pattern of microemboli observed on TCD might suggest more likely mechanisms that should be considered. For example,

emboli detected in bilateral cerebral vessels suggest either a central embolic source, such as from the heart or aorta; intravascular coagulation; or multifocal dysfunction of the endothelium. Alternatively, multiple emboli detected only unilaterally are more likely from proximal arterial disease, such as carotid atherosclerosis. Lone emboli detected during a TCD monitoring study might suggest artery to artery embolization but could also be secondary to low rates of emboli formation from central sources or systemic endothelial or coagulation dysfunction.

Our study has multiple limitations. Firstly, our study represents a small sample collected at a single institution in patients who received neurologic consultation for stroke or unexplained, refractory encephalopathy. A larger patient sample drawn from the population of hospitalized COVID-19 patients is required to determine the prevalence of circulating cerebral microemboli and the risk factors for those microemboli. The rapidly evolving landscape of COVID-19 combined with the logistical challenges of performing research in this patient population represent an opportunity for collaborative, multi-center research.[15,18] Such a multi-center study could help determine the frequency, duration, and responsiveness to therapy of microemboli in COVID-19. The logistical challenges of performing bedside evaluations in COVID-19 patients also limited the practicality of performing very prolonged TCD monitoring. However, we performed at least 60 minutes of monitoring in each patient in whom we concluded no emboli were detected, which is consistent with consensus recommendations.[16] While automated artifact detection software on TCD devices may be a helpful aide, an experienced TCD practitioner is required at the bedside to interpret doppler signals in the context of the acquisition environment; events such as patient movements, external mechanical devices, or nursing activities may produce artifacts or obscure doppler signals in a manner that cannot be easily resolved after study acquisition. Since our study used clinically obtained TCD studies, it was not possible for our study to protocolize timing of TCD studies nor to perform serial studies without clinical indication; a future multi-center prospective study might address this limitation. It should be noted that Case 1 had a thrombectomy attempt six hours prior to the TCD study. It is not possible to completely exclude the possibility that the thrombectomy procedure contributed to emboli formation; however, the observation of left-sided microemboli when the left cerebral circulation was not catheterized makes this possibility less likely. In addition, existing evidence suggests that microemboli observed after mechanical thrombectomy for stroke are more likely to represent the underlying mechanism of stroke than vascular damage related to the procedure.[17] Furthermore, it should be noted that each patient in our study had a past medical history that included risk factors for vascular disease. It is unclear from our study if underlying vascular disease or vascular risk factors are necessary for microemboli to develop in COVID-19. However, reports of large-vessel stroke in young COVID-19 patients with no major past medical history suggest that underlying vascular disease may modify the risk of emboli formation but is not likely a prerequisite.[2]

Conclusion

Circulating cerebral microemboli may occur in patients hospitalized with COVID-19 who have experienced stroke or have unexplained, refractory encephalopathy, and these microemboli can occur in the absence of severe pulmonary manifestations. Whether markers of systemic inflammation or coagulopathy can identify patients at higher risk for cerebral microemboli remains undetermined. However, our data suggest that these microemboli may be common in patients hospitalized with neurologic manifestations of COVID-19 and warrant further investigation.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2020.105542.

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