Air Medical Journal 40 (2021) 92–96

Contents lists available at ScienceDirect

Air Medical Journal

journal homepage: http://www.airmedicaljournal.com/

Critical Care Update

Coronavirus Disease 2019 and Stroke

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An association between coronavirus disease 2019 (COVID-19) and stroke has been suggested in multiple reports. When compared with historic controls admitted for influenza, COVID-19 patients had a higher incidence of stroke than patients with historic influenza. Others have observed an increased severity of stroke and higher mortality in patients with a coincident diagnosis of COVID-19. Higher stroke severity has been related to a greater propensity toward large intracranial vessel occlusion in affected patients. The increased likelihood of large vessel disease causing stroke has been associated with the thrombogenic nature of COVID-19. Endothelial injury and inflammation have also been reported as factors contributing to stroke in COVID-19 patients.

Despite the reported association between COVID-19 pathophysiology and stroke, multiple reports indicate a decreased number of patients admitted with stroke and a reduction in the use of acute therapies for this disorder. Reduced stroke volume is consistent with a decline in noninfectious emergency department (ED) visits. Despite the pandemic conditions associated with COVID-19, our hospital noted a 39% decrease in overall ED visits during the early months of the pandemic compared with a comparable time period in 2019. It remains unclear how the stroke model of care will be affected by these and other observations.

COVID-19 and Stroke

Naeimi R, Ghasemi-Kasman M. Update on cerebrovascular manifestations of COVID-19. *Neurol Sci*. 2020;41:3423-3435.

Fajgenbaum DC, June CH. Cytokine storm. *N Engl J Med*. 2020;383:2255-2273.

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Yao X, Liu S, Wang J, et al. The clinical characteristics and prognosis of COVID-19 patients with cerebral stroke: a retrospective study of 113 cases from one single center [e-pub ahead of print]. *Eur J Neurosci*. doi:10.1111/EJN.15007, accessed 12-10-20.

From the time of its presentation, COVID-19 has had a complex collection of symptoms including a varied presentation of pneumonia. Constitutional symptoms at the onset of disease include fever, dry cough, shortness of breath, sore throat, fatigue, malaise, dyspnea, and headache. More severe cases develop pneumonia, acute respiratory distress syndrome, and multiorgan dysfunction, with 15% of patients experiencing severe pneumonia and 5% of patients suffering from acute respiratory distress syndrome. Approximately one third of patients with COVID-19 present with neurologic symptoms including myalgia; impairment of taste, smell, and vision; polyneuropathy; and neuralgia. Nonspecific central nervous system effects of COVID-19 include dizziness, headache, nausea, vomiting, and languid behavior. More advanced neurologic presentation includes cerebrovascular disease, acute encephalitis, meningitis, ataxia, epilepsy, and impaired consciousness.

Evidence is increasing that COVID-19 is also associated with ischemic and hemorrhagic stroke thought to be related to the coagulopathy associated with this viral infection. Demographic reports suggest that patients with acute neurologic complaints are younger with large vessel multidistribution occlusion, more severe strokes, and the development of mobile fragile clots resistant to fibrinolysis and difficult to treat with standard mechanical thrombectomy. Although hypercoagulability associated with COVID-19 infection in critically ill patients frequently requires higher anticoagulation targets in comparison to other ill patients, adverse bleeding events make anticoagulation management challenging. Management of hypercoagulability associated with COVID-19 infection becomes important to facilitate the identification of targets for intervention to optimize treatment of this disease.

A recent review describes three distinct stages of infection related to COVID-19. First is the early infection stage in which the virus infiltrates the lung parenchyma and proliferation occurs. The immune response includes monocyte and macrophage infiltration. Second is what is described as a pulmonary phase. This phase includes tissue injury, vasodilation, endothelial permeability increase, and leukocyte recruitment in association with inflammation. Third is the hyperinflammation phase characterized by worsening inflammatory response even if the viral burden has decreased. Most cases of infection secondary to COVID-19 are mild or asymptomatic, with some patients developing limited constitutional symptoms including the sensation of respiratory distress and hypoxemia. Notably, in patients in whom manifestations of disease worsen, lymphocytopenia is observed in association with an increased cytokine burden. As the disease progresses, patients with COVID-19 infection may develop both arterial and venous thromboembolism. Hematologic outcomes include thrombocytopenia and elevated D-dimer. Other coagulation findings include prominent presentation of fibrin and fibrinogen degradation products. Prothrombin time, partial thromboplastin time, and platelet count abnormalities are uncommon during the initial presentation. However, with progression of

1067-991X/$36.00

https://doi.org/10.1016/j.amj.2020.12.003

the disease, coagulation cascade activation with procoagulant and anticoagulant imbalance is seen through viral stimulation of systemic inflammation including increased systemic fibrin clot formation, microthrombosis, and disseminated intravascular coagulation coinciding with multiorgan failure. Atherosclerotic plaque rupture related to local inflammation and cytokine release is thought to be related to arterial thromboembolism and large vessel occlusion causing stroke.

A number of inflammatory markers have been detected in advanced critical illness related to COVID-19 infection. These include interleukin (IL)-2, IL-6, tumor necrosis factor alpha, interferon gamma, monocyte chemoattractant protein-1, macrophage inflammatory protein-1 alpha, granulocyte colony-stimulating factor, C-reactive protein, procalcitonin, and ferritin. In addition to gas exchange compromise, pulmonary circulation is affected by microthrombosis, which could contribute to central hypoxia mediated through the respiratory center in the brainstem, leading to reduced effectiveness of oxygen metabolism. In addition to a reduced oxygen supply, oxygen demand increases with transition to anaerobic metabolism, cerebral vasodilation, pulmonary vasoconstriction, and unstable hemodynamics. Cardiac embolization due to virus-related injury occurs in 20% to 30% of hospitalized patients with evidence of myocarditis and cardiomyopathy including elevated cardiac injury markers and signs that the heart is a potential target of systemic inflammation.

Antiphospholipid antibodies, another product of inflammation, have been associated with acute stroke in COVID-19 patients. Evidence here is still evolving, but overall thromboembolic events affecting brain function may occur through a combination of conditions including blood flow stasis due to immobilization in critically ill patients, underlying coagulopathy, and damage to the endothelium related to viral infection. Early reports from China document a combination of respiratory and neurologic complaints in patients with COVID-19 infection. Unfortunately, many of these patients were not candidates for thrombolysis or other neurologic interventional procedures during acute hospitalization. Patients with evidence of cerebral ischemia had laboratory findings consistent with excessive inflammation and a tendency toward thrombosis.

A larger case-control study including 41 patients with imaging suggestive of acute cerebral infarction and 82 controls from New York City revealed that 43% of strokes were in individuals with concurrent COVID-19 infection, whereas 18.3% of patients without positive cerebral imaging were affected by COVID-19 infection. COVID-19 infection had a significant independent association with acute ischemic stroke leading this group to recommend more aggressive monitoring for stroke in COVID-19 patients. Another single-center, prospective study described a mean fall of 38% in incidence for new stroke diagnosis but reported a larger rate of new large vessel occlusion associated with strokes when identified. This report suggested that the proportion of new large vessel occlusion stroke doubled with coincident COVID-19 infection.

Details in a recent case report discuss the subtypes of stroke and mechanisms in patients experiencing COVID-19 infection. Coagulopathy and inflammation are central to thrombosis within cerebral vessels and cardiac embolism, two of the major mechanisms of ischemic stroke in COVID-19 patients. Various mechanisms of stroke and sources of cardiac embolism have been suggested. Patients with COVID-19 infection may have a higher risk of stroke because of coexisting factors including advanced age, preexisting cardiovascular disease, inadequate medication availability, and cerebral microvascular changes. Cross talk between coagulopathy and inflammation is suggested by a reported elevation in D-dimer, fibrinogen, lupus anticoagulant, presentation with sepsis, cytokine storm markers, and an elevation in C-reactive protein levels. Large and small vessel occlusion may occur with in situ thrombosis, cardiac embolism, or endothelial inflammation causing vasculitis. Of the occlusive insults described, the majority are related to large vessel effects. Ten percent of patients are noted to have intracranial hemorrhage, which has been related to hypertension, vasculitis, and consumptive coagulopathy. Cardiac embolism has multiple potential contributing mechanisms. These include endocarditis related to secondary infections; cardiac arrhythmia possibly related to an infectious etiology; toxic effects of drugs; and the development of left ventricular mural thrombus secondary to myocardial injury related to hypoxemia, hypertension, catecholamine excess, or frank myocardial infarction.

COVID-19–Related Stroke in the Young

Fifi JT, Mocco J. COVID-19 related stroke in young individuals. *Lancet Neurol*. 2020;19: 713-715.

Bekelis K, Missios S, Ahmad J, et al. Ischemic stroke occurs less frequently in patients with COVID-19: a multicenter cross-sectional study. *Stroke*. 2020;51: 3570-3576.

COVID-19 has been associated with a 7.6-fold increase in the odds of stroke compared with historic influenza. The reported incidence of cerebrovascular disease in patients testing positive for COVID-19 ranges from 1% to 6%, which may translate to large numbers of individuals as the pandemic progresses. Multiple regions with a high COVID-19 prevalence have reported a stable or increased incidence of large vessel stroke and an increased incidence of cryptogenic stroke (patients with none of the typical causes of stroke) despite having a decrease in reports of mild strokes possibly related to quarantine and self-isolation. Other groups have observed stroke development in patients younger than 50 years of age who tested positive for COVID-19 with no vascular risk factors. These individuals were often admitted to the hospital with large vessel stroke. A 7-fold increase in the rate of large vessel stroke in young people has been seen compared with other time intervals. Younger patients had laboratory findings consistent with hypercoagulable states, leading to consideration that stroke was likely related to the presence of COVID-19 vasculopathy. With time, the observation of COVID-19 –related stroke in young patients has been supported by data presented from other centers around the world. A study of thrombectomy cases included a mean age of 52.8 years from New York City and 59.5 years from Paris and a similar series of cases from Philadelphia. These ages are younger than the typical population requiring thrombectomy procedures. Another analysis of acute stroke protocol imaging from New York revealed that after adjusting for age, sex, and vascular risk, the presence of COVID-19 was independently associated with stroke. Other reports suggest that stroke may present as an initial symptom of patients with COVID-19 infection in the presence of minimal respiratory changes.

These data are contradicted by a large cross section of patients using a large health care system in New York, which did not identify an increased likelihood of stroke on presentation among patients of all ages with COVID-19 infection. However, patients experiencing stroke with concurrent COVID-19 infection demonstrated increased mortality and a trend toward an increasing need for rehabilitation after presentation with stroke. This study did not support the concern for increased stroke risk in the young. Remarkably, these investigators identified a decrease in stroke admissions when pandemic activity was at its peak. They associate this finding with other reports describing “vanishing strokes and heart attacks” during the pandemic. Stroke experts have attributed this phenomenon to the unwillingness of neurologic patients to be exposed to COVID-19 when EDs were overwhelmed. In addition, there is some experimental evidence that IL-6, which is elevated in COVID-19, may have a

neuroprotective effect and enhance angiogenesis. Low platelet counts, which have been reported in the setting of COVID-19 inflammation, may reduce the formation of large clots in intracranial circulation. Finally, the report from New York identified a higher risk of an unfavorable outcome in patients with ischemic stroke infected with COVID-19, independent of traditional stroke risk factors and surrogates for stroke severity. The observed mortality for COVID-19–positive patients with stroke was nearly 32% in the New York study compared with 4.6% for COVID-19–negative patients with stroke.

Where Have the Stroke Patients Gone?

Jeffery MM, D'Onofrio G, Paek H, et al. Trends in emergency department visits and hospital admissions in health care systems in 5 states in the first months of the COVID-19 pandemic in the US. *JAMA Intern Med*. 2020;180:1328-1333.

Kansagra AP, Goyal MS, Hamilton S, Albers GW. Collateral effect of Covid-19 on stroke evaluation in the United States. *N Engl J Med*. 2020;383:400-401.

Westgard BC, Morgan MW, Vazquez-Benitez G, Erickson LO, Zwank MD. An analysis of changes in emergency department visits after a state declaration during the time of COVID-19. *Ann Emerg Med*. 2020;76:595-601.

One remarkable effect of the pandemic is a decrease in patients presenting for evaluation of cerebrovascular disease and treatment of stroke. A multistate survey performed over the first half of 2020 found that ED visit counts decreased, and the rates of hospital admission from the ED increased over the same time interval. In this survey, ED visits decreased by more than 40% over multiple health care systems and by more than 60% in New York, a site where the pandemic was most acute. The rates of hospital admission from the ED were stable until COVID-19 cases increased locally, suggesting lower patient volume and higher acuity in the ED as the COVID-19 pandemic spread. Despite different timing and increased rates of COVID-19 cases locally, these investigators observed similar patterns and timing of ED visits across multiple states and health care systems, with the steepest decline in visits beginning in mid-March 2020. A possible explanation for these temporal patterns was the public response to national risk messaging about COVID-19 rather than changes in the local situation with regard to reported COVID-19 cases. This writing group also postulated that individuals may have avoided seeking ED care because of a fear of being exposed to COVID-19 in the ED, concerns about the possibility of extended wait times, or a sense of responsibility to avoid using health care services that others may have needed. Even as ED visits decreased most rapidly during the initial phase of this study, the usual admission rates from the ED were stable, indicating that admission counts were decreasing as well. However, ultimately, a temporal association was found between the increase in each state's COVID-19–related caseload and admission rates. This trial did not attempt to identify ED visits as possibly associated with COVID-19; thus, it did not directly examine the decrease in non–COVID-19 ED visits.

A brief report describing a surrogate for stroke care examined a commercial neurologic imaging monitoring database with a software platform as a surrogate for quantity of care that hospitals provided to patients with acute symptoms of stroke. The software system was designed to select patients who could benefit from endovascular thrombectomy by identifying occlusion of major cerebral arteries or regions of the brain with potentially reversible ischemia that had not infarcted. Investigators had access to data on over 231,000 patients who underwent imaging processed with the software system described previously in over 800 hospitals in the United States between July 2019 and April 2020. This team compared the mean daily counts per hospital of patients in the software system in a pre-pandemic 29-day interval in comparison to a 14-day time interval during the early pandemic extending between March and April 2020. During the study interval before the pandemic, the number of patients per hospital who underwent imaging was similar to baseline numbers reflecting hospital activity before the pandemic. During the pandemic, the number of patients who underwent imaging, as reflected by examination of the software package, decreased by 39% per day per hospital compared with the interval prior to the pandemic. The decrease in the use of stroke imaging from before to during the pandemic was seen across all age, sex, and stroke severity subgroups. This pattern suggested a decrease in the number of evaluations both in patients with severe strokes and in nonelderly patients who may have been at lower risk for COVID-19 complications. A reduction in the number of patients who underwent stroke imaging was seen across multiple states and a range of hospital sizes. These data suggested that differences in the regional incidence of COVID-19 were not a primary cause of decreased use of stroke imaging.

A more recent observational study examined demographics, visit characteristics, and diagnoses for all ED patients visiting an urban level 1 trauma center before and after a state of emergency declaration and compared this ED usage data with a similar interval in 2019. The investigators estimated the percent change based on the ratios of before and after periods with respect to 2019 and the decline in visits per week using regression analysis. Finally, the team evaluated each factor that appeared to modify the change in overall ED visits. After the state declaration of emergency due to the COVID-19 pandemic, there was a 49.3% decline in ED visits overall and a 35.2% reduction compared with 2019. A disproportionate decline was noted in visits by pediatric and older patients, women, and Medicare recipients as well as for presentation of syncope, cerebrovascular accident, urolithiasis, abdominal, and back pain. Significant proportional increases were observed in ED visits for upper respiratory infections, shortness of breath, and chest pain. Investigators in this single-site trial recommend additional effort to understand these phenomena and encourage appropriate care seeking while identifying the potential morbidity and mortality that could result from delayed or deferred care. As the authors discuss, the most concerning finding in this study was the overall decline in patients seen for acute and possibly life-threatening conditions unrelated to COVID-19 infection. They found a disproportionate decline in visits for conditions with substantially higher acuity including cerebrovascular disease. A review of this and other data suggest that the stroke patients have remained at home until the severity of symptoms led them to present to the hospital.

Breaking the Chain

Montaner J, Barragán-Prieto A, Pérez-Sánchez S, et al. Break in the stroke chain of survival due to COVID-19. *Stroke*. 2020; 51:2307-2314.

Hsiao J, Sayles E, Antzoulatos E, et al. Effect of COVID-19 on emergent stroke care: a regional experience. *Stroke*. 2020;51: e2111-e2114.

Zhao J, Li H, Kung D, Fisher M, Shen Y, Liu R. Impact of the COVID-19 epidemic on stroke care and potential solutions. *Stroke*. 2020;51:1996-2001.

We are all well aware of emergency measures in place to treat patients with

COVID-19 and contain the outbreak. This is the major priority of many hospitals. It is also important to consider the collateral damage of this crisis on patients with other acute diseases. Previous coronavirus outbreaks, such as the one South Korea experienced in 2015 due to Middle East respiratory syndrome, resulted in changes in emergency care use. In that situation, the number of emergency room visits during the peak of the Middle East respiratory syndrome epidemic decreased by over 33% and was more pronounced for low acuity diseases (> 50%) than for high acuity diseases such as myocardial infarction (14%) or stroke (>16%). Similarly, the COVID-19 outbreak has been shown to affect cardiovascular disease, with an abnormally small number of patients with acute myocardial infarction seeking medical help after the establishment of infection control measures. A report from Hong Kong suggests that patients are reluctant to go to a hospital during the COVID-19 outbreak, which explains the potential delays in seeking care. They also report delays in evaluating patients with myocardial infarction after hospital arrival. A report from a regional stroke care system in Spain suggests that the COVID-19 pandemic is disrupting stroke care across the globe as multiple elements of the stroke chain of survival are interrupted.

The Spanish report documents a clear reduction in the number of acute stroke cases attended and treated by hospitals in a regional stroke treatment network with reduced effectiveness of stroke activity outside the hospital (telestroke and ambulance transfers). Stroke care centers in Spain reported a reduction in admitted cases of 25%, largely reflected in a reduction in ischemic stroke cases. A reduction in hemorrhagic stroke was also seen, but the difference was not statistically significant. Spanish investigators also observed a 40% reduction in the number of patients seen with transient ischemic attacks in the ED. Similarly, the mean time of arrival at the hospital from symptom onset among patients admitted to stroke units was delayed more than half an hour. A statistically significant decrease in reperfusion therapies including thrombolytic agents and thrombectomies was observed, likely reflecting the smaller number of patients presenting in a timely manner with relevant complaints.

Consultations to the telestroke network supported by these centers decreased dramatically. Similarly, patients who were connected by telestroke teams with reperfusion therapies declined from 29% of patients among consults received to 16% of consults received after the outbreak of COVID-19. Notably, a trend toward increased stroke severity was observed among patients attended in the telestroke network. Unfortunately, large delays from symptom onset to hospital arrival time occurred, particularly with smaller hospitals covered through telestroke, with an increase in prehospital time of greater than 1 hour. Stroke centers in this report were forced to put multiple protective measures in place based on the assumption that a code stroke patient was potentially infected with COVID-19. For example, after head computed tomographic imaging, chest computed tomographic imaging was also performed in all acute stroke cases to identify lung infiltrates leading to the transfer of patients to the respiratory units of the hospital waiting for COVID-19 confirmatory testing. For patients undergoing procedures, protection protocols reduced the use of anesthesia and intubation to avoid aerosol generation. Finally, the need to maintain the availability of ambulance services for COVID-19 led to a reduction of available units for the transfer of patients with acute neurologic symptoms consistent with stroke. Ironically, this report from the Seville region in Spain originates from a well-equipped and sophisticated stroke community. The authors expressed concern that rural areas dependent on telestroke and rapid patient transfer were more severely affected. The Seville team suggests that acute vascular disease probably killed more patients than COVID-19 during the interval of this study.

A brief report from the United States reveals similar concerning findings. A 3-state region in the central portion of the country witnessed a 39% reduction in stroke consultation with an associated 31% reduction in various reperfusion therapies. During this time, bed utilization data revealed that health care systems were not overwhelmed. A similar set of public health concerns are raised by the Spanish and American investigators. They echo concern that stroke patients are not seeking emergent care, frequently presenting 24 hours after the onset of symptoms or not seeking acute care at all. Even severe strokes were at times receiving less or delayed reperfusion therapy. With ongoing stay-at-home orders, these writers fear that the reduction in stroke care may persist or worsen.

The most dramatic report describing the impact of COVID-19 on stroke care comes from over 200 stroke centers in China. Data were generated from the Big Data Observatory Platform consisting in total of 280 hospitals across China providing stroke care. The vast majority of centers were able to provide complete data. Similar to the smaller reports discussed previously, reperfusion therapies were reduced by over 26%, and the capacity for stroke care was noted to be dramatically affected in the majority of reporting hospitals. Most of the stroke centers stopped or reduced stroke education for the public. Hospital admissions related to stroke were reduced by 40%. Reduced admissions and prehospital delays were noted with an emphasis on a lack of stroke knowledge and proper transportation cited as significant limiting factors.

Based on the data from these reports, Zhao et al made a set of recommendations regarding stroke care during the COVID-19 pandemic. First, stroke awareness during the crisis is essential. Education activities should be enhanced rather than reduced. In the setting of a pandemic, education should be available to inform patients how to address symptoms. Second, fast-track COVID-19 screening for patients with potential stroke is needed. This includes the availability of chest computed tomographic scan data and rapid laboratory testing for the virus so that essential stroke treatment is not delayed. Third, patients should wear surgical masks or take other measures for infection source control following hospital policies developed in conjunction with infectious disease services to protect both patients and medical staff. Fast-track stroke care via various modalities should remain available. Finally, national medical policy should reflect the need to maintain quality care for emergent, treatable, time-sensitive diseases such as stroke and myocardial infarction even in the setting of the COVID-19 pandemic.

Summary Points

- COVID-19 presents with a combination of exaggerated inflammation and thrombosis. One of the vascular beds targeted by this systemic process is the intracranial circulation. Unfortunately, large vessels are frequently affected by COVID-19, and large vessel strokes tend to be resistant to standard reperfusion therapies.
- Patients seeing the most severe effects of COVID-19 also have underlying medical problems placing them at risk for stroke, such as obesity, diabetes, and other cardiovascular disease. A number of reports suggest that patients with COVID-19 and coincident stroke have far higher morbidity than individuals without this combination of insults. COVID-19 has an associated increase in the odds of stroke 7 times greater than historic influenza. Large data sets also report mortality with stroke is at least

6 times greater in patients who are positive for COVID-19 than in individuals in whom the virus has not been found.

- One of the most concerning findings in systems for stroke care is delay or failure of presentation for patients with suspicious symptoms. With a focus on COVID-19, many individuals simply remain at home. A growing number of reports suggest a delay in care due to a reduced use of essential imaging and interventional therapies.
- Multiple recommendations come from recent demographic studies. Most important is continued stroke awareness, education, and availability of acute resources, which allow rapid assessment for both stroke and COVID-19. Stroke care must progress during and with precautions to mitigate COVID-19 risk. In addition, telestroke and transport services must retain capacity to facilitate rapid access of patients at risk to stroke care centers.

Acknowledgment

The authors gratefully acknowledge the assistance of Ms. Sherry Willett in preparation of this series for *Air Medical Journal*.

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