Cerebrovascular Accident and SARS-CoV-19 (COVID-19): A Systematic Review

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Keywords

COVID-19 · Coronavirus · Cerebrovascular attack · Stroke

Abstract

Background: While the most common neurologic symptoms reported in patients affected by SARS-CoV-2 are headache, dizziness, myalgia, mental fog, and anosmia, there is a growing basis of published peer-reviewed cases reporting stroke in the setting of SARS-CoV-2 infection. The peer-reviewed literature suggests an increased risk of cerebrovascular accident (CVA) in the setting of COVID-19 infection.

Methods: We searched 3 databases (PubMed, MEDLINE, and CINAHL) with search terms COVID-19, novel coronavirus, stroke, and cerebrovascular accident. Case series and case studies presenting patients positive for both COVID-19 and CVA published from January 1 through September 1, 2020, were included. Data collection and analysis was completed and risk of bias assessed. **Results:** The search identified 28 studies across 7 counties comprising 73 patients. Amongst patients hospitalized for COVID-19 infection and CVA, the average age was 60; the most common preexisting conditions were hypertension and diabetes mellitus, and those without preexisting conditions were significantly younger with an average age of 47. Amongst hospitalized patients with COVID-19 and CVA, there was a bimodal association with COVID-19 infection severity with majority of patients classified with mild or critical COVID-19 infection. **Discus-**

sion: The data suggest SARS-CoV-2 is a risk factor for developing stroke, particularly in patients with hypertension and diabetes. Furthermore, the younger average age of stroke in patients with SARS-CoV-2, particularly those patients with zero identifiable preexisting conditions, creates high suspicion that SARS-CoV-2 is an independent risk factor for development of stroke; however, this cannot yet be proven without comparable control population. The data suggest the risk of developing CVA in the setting of COVID-19 infection is not dependent upon severity of illness. Continued studies must be done to understand the epidemiologic factors of COVID-19 infection and stroke and the pathophysiology of the COVID-associated hypercoagulable state.

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Introduction

As of October 2020, novel coronavirus, or COVID-19 infection by the SARS-CoV-2 virus, had an impact of over 35 million confirmed cases and 1 million deaths worldwide [1]. While SARS-CoV-2 most commonly affects the lungs causing bilateral pneumonia, respiratory failure, and acute respiratory distress syndrome, a wide variety of neurologic findings have been associated with the virus [2]. The most common neurologic symptoms reported in patients affected by SARS-CoV-2 are headache, dizziness, myalgia, mental fog, and anosmia [3, 4]. Additionally,

there is a growing basis of published peer-reviewed cases reporting stroke and SARS-CoV-2 infection. A systematic review found that patients with a past medical history of stroke were 3 times more likely to die of COVID-19 but concluded stroke is not a complication of COVID-19 [4]. Two separate studies found that the incidence of stroke in patients with confirmed COVID-19 was between 5 and 5.7% in small community hospitals in Wuhan, China [5, 6]. These patients were associated with severe illness, risk factors such as hypertension, diabetes, and history of coronary artery disease, or prior cerebrovascular disease [5].

The peer-reviewed literature suggests an increased risk of stroke or cerebrovascular accident (CVA) in the setting of COVID-19 infection [4, 5]. However, the nature of this association remains to be elucidated. Whether risk of stroke in the setting of COVID-19 infection is independent of age, severity of infection, and comorbidities is not well documented within the literature. Our goal was to conduct a systematic review to better understand the clinical picture and presentation of patients with stroke and confirmed

COVID-19 infection and to assess comorbid risk factors associated with stroke and COVID-19 such as age, sex, severity of COVID-19 infection, and past medical history.

Methods

Search Strategy and Selection Criteria

Our methods adhere to the guidelines established by PRISMA. We conducted a systematic review in the following databases: PubMed, MEDLINE, and CINAHL. Search terms included COVID-19, novel coronavirus, stroke, and cerebrovascular accident. There were no language restrictions used during literary search. The last search was performed from January 1, 2020, through September 1, 2020.

Inclusion Criteria

Articles that addressed the clinical case of COVID-19-positive patients, with confirmed diagnosis of stroke with imaging studies positive, were included. Only case reports or case series published in full text with peer reviews were included in data review. Published, peer-reviewed case reports or case series found under the aforementioned search terms were included.

Fig. 1. PRISMA flow diagram.

Table 1. Study characteristics [8–35]

First author	Case type	Country	N	Age, years	Female, N	Presenting symptom	COV severity	Images included	Past medical history	Stroke treatment
Acharya et al. [13]	Case report	USA	1	60	0	COV	Critical	nr	Present	nr
Al Saiegh et al. [14]	Case series	USA	2	46.5	1	COV (1); CVA (1)	Mild (1); asymptomatic (1)	CT (2)	NPMH (1), NR (1)	Stent placement (1); decompressive hemicraniectomy, EVD placement
Avula et al. [15]	Case series	USA	4	81	3	CVA (4)	Critical (3); mild (1)	CT (3); MRI (1)	Present (4)	ASA (1); no treatment (2); ASA, statins (1)
Ballvé-Martín et al. [16]	Case report	Spain	1	40	1	COV	Severe	CT, CTA	NPMH	Mechanical thrombectomy
Barrios-López et al. [17]	Case series	Spain	4	71	2	CVA (3) COV (2)	Critical (2), moderate (1), asymptomatic (1)	CT(2)	Present (3); NPMH (1)	Intravenous fibrinolysis (1); anticoagulation (1)
Beyrouti et al. [18]	Case series	United Kingdom	6	69.8	1	COV (1); COV/ CVA (5)	Moderate (1); severe (3); critical (1); mod-severe (1)	nr (6)	Present (5); NPMH (1)	ASA, clopidogrel, LMWH, LMWH (1); external ventricular drainage, LMWH (1); apixaban (1); LMWH (1); intravenous thrombolysis (2)
Co et al. [19]	Case report	Philippines	1	62	1	COV	Moderate	CT	Present	Intravenous thrombolysis, ASA
Deliwala et al. [20]	Case report	USA	1	31	1	COV	Critical	CT	NPMH	Atorvastatin, ASA
Doo et al. [21]	Case series	USA	2	59.5	0	COV (1); CVA (1)	Mild (1), critical (1)	CT (2); MRI (1)	Present (2)	Eptifibatide (1); antiepileptic drugs (1)
Dumitrascu et al. [22]	Case report	USA	1	48	0	COV	Critical	nr	Present	Enoxaparin, LMWH
Elshereye et al. [23]	Case report	USA	1	75	1	CVA	Critical	CT/MRI	Present	ASA, statin
Fara et al. [24]	Case series	USA	3	55	2	CVA (3)	Moderate (2), mild (1)	CT (3)	nr (1); present ASA, clopidogrel, apixaban (1); (1); NPMH enoxaparin, ASA, clopidogrel, warfarin (1); eptifibatide, heparin (1)	
Gill et al. [25]	Case report	USA	1	79	1	CVA	Critical	CT/MRI	Present	Thrombectomy
Goldberg et al. [26]	Case report	USA	1	64	0	CVA	Critical	CT	Present	nr
Klein et al. [27]	Case report	USA	1	29	1	CVA	Mild	CT/MRI	NPMH	Enoxaparin, lorazepam, levetiracetam
Mahboob et al. [28]	Case report	USA	1	58	1	CVA	Critical	CT/MRI	Present	ASA, statin, osmotic therapy with hypertonic saline
Morassi et al. [29]	Case series	Italy	6	68.5	1	COV (1)	Severe (5); moderate (1)	CT (6); MRI (1)	Present (5); NPMH (1)	ASA, clopidogrel, enoxaparin, levetiracetam
Oxley et al. [30]	Case series	USA	5	40.4	1	CVA (5)	Mild (3), asymptomatic (2)	nr (5)	Present (3); NMPH (2)	Apixaban (1); clot retrieval, apixaban (1); clot retrieval, ASA (1); alteplase, clot retrieval, hemicraniectomy, aspirin (1); clot retrieval, stent, ASA, clopidogrel (1)
Papi et al. [31]	Case report	Italy	1	79	1	CVA	Asymptomatic	CT	Present	Thrombectomy
Reddy et al. [32]	Case series	USA	12	48.3	2	COV (2); CVA (2)	Critical (1); mild (1); moderate (1); asymptomatic (1); NR (8)	CT (4)	nr (4)	Anticoagulation, antiplatelet therapy, intravenous thrombolysis, mechanical thrombectomy

Table 1 (continued)

First author	Case type	Country	N	Age, years	Female, N	Presenting symptom	COV severity	Images included	Past medical history	Stroke treatment
Rudilosso et al. [33]	Case report	Spain	1	50	0	COV	Moderate	CT/MRI	NR	Heparin, IVC filter
Saggese et al. [34]	Case report	Italy	1	62	0	CVA	Moderate	CT	Present	Alteplase therapy
Sangalli et al. [35]	Case series	Italy	4	66	1	Stroke (3); COV/CVA (1)	Mild (1); critical (1); severe (2)	nr (4)	Present (4)	Alteplase (2); intravenous thrombolysis (2)
Tunc et al. [36]	Case series	Turkey	4	65.3	2	COV/CVA (4)	Moderate (4)	CT/MRI (4)	Present (4)	ASA, LMWH (2); ASA, clopidogrel (2)
Valderrama et al. [37]	Case report	USA	1	52	0	COV/CVA	Mild	CT	Present	Alteplase, mechanical thrombectomy
Wang et al. [38]	Case series	USA	5	nr	nr	CVA (5)	nr (2); death (3)	CT (2)	Present (3); NPMH (2)	Endovascular thrombectomy (5)
Zahid et al. [39]	Case report	USA	1	38	0	COV	Critical	CT	NPMH	nr
Zhai et al. [40]	Case report	China	1	79	0	COV/CVA	Mild	CT (1)	NPMH	Clopidogrel, atorvastatin

ASA, aspirin; COV, coronavirus-19 infection; CVA, cerebrovascular accident; CT, computerized tomography; CTA, computerized tomography with angiography; LMWH, low-molecular-weight heparin; MRI, magnetic resonance imaging; nr, not reported; NPMH, no past medical history.

Table 2. Patient characteristics

Studies, <i>n</i>	28
Patients, <i>n</i>	73
Average patient age±standard deviation, years	60±16
Female sex, %	42
Presenting symptom COVID, %	50

Exclusion Criteria

No article earlier than 2020 was considered. Literature reviews, commentaries, and case reports on stroke rule outs were excluded.

Data Collection and Risk of Bias Assessment

Screening by title and abstract was conducted independently by 2 investigators (A.A. and I.D.). Full-text review was conducted independently by all authors. Data abstraction was conducted independently by 2 investigators (A.A. and A.P.) using a standardized form shared between all authors. A third investigator resolved any differences of opinion in data gathering (I.D.).

Outcomes of interest in the study included clinical picture on presentation to care, age, sex, past medical history, infection severity, and treatment modalities. Severity of COVID-19 infection was determined by standards outlined by the WHO [7]. Data collected included first author, type of article, country of publication, number of patients, age, sex, COVID-19 severity, included imaging, presenting symptom, and past medical history including prior CVA, coronary artery disease, hypertension, hyperlipidemia, obesity, diabetes, chronic kidney disease, and atrial fibrillation.

Risk for bias in data extraction was found to be minimal as the majority of data extracted were empirical in nature. Standardized published guidelines were used to assess COVID-19 severity based on published qualitative symptomatology [7].

Data Analysis

Means, percentages, and standardized deviations were calculated in Google Sheets. Statistical analysis comparing average ages amongst independent variables was analyzed using 1-tailed, independent *t* test analysis through VassarStats. Qualitative data were summarized through counts in Google Sheets.

Results

Initial search yielded 71 studies. After removing 29 duplicates, 42 articles were reviewed by abstract and title. Publications identified to be reviews, commentaries, and case reports with stroke rule outs were excluded. After initial screen, 28 articles met inclusion criteria and subsequently underwent full-text review (Fig. 1).

Of the 28 articles assessed, 16 were case reports and 11 case series (Table 1). Seven countries were represented in the published studies: USA (17), Spain (3), Italy (3), United Kingdom (1), Philippines (1), Turkey (1), and China (1) (Table 1). Across all articles, 73 patients were

Fig. 2. Average age of patients hospitalized for COVID-19 infection and CVA. CVA, cardiovascular accident; F, female; M, male; NPMH, no past medical history; PMH, past medical history.

Fig. 3. Average age and presenting symptom of patients hospitalized for COVID-19 infection and CVA. CVA, cardiovascular accident; COV, COVID-19; F, female; M, male.

assessed, of which 42% were females (Table 2). The average age of the study population was 60 years (Table 2; Fig. 2).

No statistical difference was seen in average age between males and females who were hospitalized with COVID-19 and CVA (Fig. 2; $p = 0.97$). Of the patients hospitalized with COVID-19 infection and CVA, those with no past medical history were significantly younger than those with one or more underlying medical conditions, with an average age of 47 as compared to 64, respectively (Fig. 2; $p < 0.01$). Nevertheless, of the study population, only 23% had no past medical history (Fig. 3). Of note, the most common comorbid conditions were hypertension and diabetes mellitus, at 52 and 36%, respectively (Fig. 3).

Amongst hospitalized patients with COVID-19 and stroke, 50% presented to care for COVID-19 infection and were subsequently found to have stroke while 50% presented to care for symptoms of stroke and were subsequently found to be positive for COVID-19 infection (Table 2; Fig. 3). There was no statistical difference in age between patients with presenting symptom of COVID-19 as compared to those with presenting symptom of CVA (Fig. 3; $p = 0.88$). Amongst hospitalized patients with COVID-19 and CVA, there was a bimodal distribution of COVID-19 infection severity, as defined by the WHO, with the majority of patients classified with either mild or critical illness; a minority of patients presented were asymptomatic or presented with moderate-severe illness (Fig. 5).

Fig. 4. Number of patients hospitalized for COVID-19 infection and CVA as stratified by past medical history and sex. CVA, cardiovascular accident; CAD, coronary artery disease; HTN, hypertension; HLD, hyperlipidemia; Obs, obesity; DM, diabetes mellitus; CKD, chronic kidney disease; AF, atrial fibrillation; NPMH, no past medical history.

Fig. 5. Number of patients hospitalized with COVID-19 and CVA as stratified by COVID-19 infection severity. CVA, cardiovascular accident.

Discussion

A COVID-19-induced hypercoagulable state has been well documented in the peer-reviewed literature; however, most cases suggest an increase in predominantly venous thromboembolic events such as deep vein thromboses and life-threatening pulmonary embolism [36, 37]. There is some emerging evidence of increased arterial dysfunction, with COVID-19-associated myocardial infarction/acute coronary syndrome and pulmonary intravascular coagulopathy [38, 39]. The current study further suggests a COVID-19-induced intravascular coagulopathy with increased risk for arteriolar thromboembolic events including CVA.

According to the American Heart Association, the average age of stroke is 65 [40]. While our systematic review

cannot be compared to the national average as the patient populations differ in size, country of origin, and setting, it is notable that the average age of patients hospitalized for COVID-19 and CVA is younger than the national average for stroke. Furthermore, patients hospitalized for COVID-19 and CVA without prior comorbid conditions were significantly younger than the national average.

The prevalence of preexisting conditions noted by the study was relatively unsurprising, as they reflect the prevalence within the general population with the highest prevalence of hypertension and diabetes mellitus (Fig. 4). The data suggest the risk of developing CVA in the setting of COVID-19 infection is not dependent upon severity of illness (Fig. 5). This finding is contrary to the peer-reviewed literature, which has suggested risk of CVA in the

setting of COVID-19 infection to be associated with critical illness [5].

The nature of our systematic review does not allow the study population to be adequately compared to a control population, and therefore an independent risk for developing stroke in the setting of COVID-19 infection could not be isolated. It remains to be seen whether the association between COVID-19 infection and stroke is causal in nature. Additional drawbacks to the study include a limited sample size with high variance. Continued studies must be done to understand the epidemiologic factors of COVID-19 infection and stroke and the pathophysiology of the COVID-associated hypercoagulable state.

Conclusions

The data suggest SARS-CoV-2 is a risk factor for developing stroke, particularly in patients with hypertension and diabetes. Furthermore, the younger average age of stroke in patients with SARS-CoV-2, particularly those patients with zero identifiable preexisting conditions, creates high suspicion that SARS-CoV-2 is an independent risk factor for development of stroke.

In the setting of the global coronavirus pandemic, patients younger than 65 years old, particularly those without risk factors for stroke, who present with CVA should be treated as a patient under investigation for SARS-CoV-2 with proper precautionary measures put in place. Furthermore, patients with known COVID-19 infection with acute change in mental status or sudden onset of focal neurological deficit should be highly concerning for SARS-CoV-2-associated CVA and should be immediately assessed for stroke. Additionally, patients with SARS-CoV-2, particularly those with hypertension, diabetes, hyperlipidemia, or prior CVA, should have neurological assessments regularly to ensure any possible stroke is diagnosed and managed.

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Statement of Ethics

The authors ensure all ethical standards were upheld in the process of research and writing the manuscript. The research did not require ethical approval as the data used are completely HIPAA protected, publicly available, and previously published. No human subjects were used, contacted, or in any way comprised in the research.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Amira Athanasios is the Principle Investigator. Ivy Daley is the co-investigator. Anjali Patel is the co-investigator. Olu Oyesanmi is the co-investigator.

Data Availability Statement

Publicly available datasets were used in this study. All data used can be found in the specific references. All data analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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