Cerebrovascular Disease Associated with the Coronavirus

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Jason Hinman, MD, PhD

☒ I have no relevant financial relationships to disclose.

OR

☑ I have these relevant financial relationships to disclose:
Outline

Historical context of coronavirus infections and neurologic disease

Review the literature associating Sars-CoV-2 infection and stroke

Proposed mechanisms of stroke in COVID-19

Management of COVID-19-related strokes

Vaccine-related cerebral venous thrombosis
Sars-CoV-1 and Stroke: A Test Run

Same coronavirus family as Sars-CoV-2

8098 total cases of Sars-CoV-1 worldwide in 2003-2004

774 deaths

206 of the cases occurred in Singapore

5 cases of large artery stroke

Fig. 1 Case 1. Computed tomography showed cerebral infarction involving the left posterior and middle cerebral artery territories with haemorrhage conversion (arrow)

Fig. 2 Case 2. Computed tomography showed right middle cerebral artery infarction with cerebral oedema and mass effect. An older left posterior watershed infarction was also noted (arrow)

Fig. 3 Case 3. Computed tomography showed extensive cerebral infarction involving both middle cerebral and left posterior cerebral arteries
The Russian Flu Pandemic of 1890s
Was the Russian Flu Pandemic (1889-1890) caused by a coronavirus (OC43)?

Coronavirus Family

Molecular Clock Analysis

Russian Flu Pandemic of 1892

Vijgen et al J. Virol 2005
To Live and Die in L.A.

LA County – COVID-19 cases

New reported cases

Vaccinations

- FULLY VACCINATED
  - All ages: 72%
  - 5 and up: 76%
  - 65 and up: 85%

See more details »

3% of vaccinations statewide did not specify the person's home county.

- About this data

Latest trends

- Cases have decreased recently but are still high.
- The numbers of hospitalized Covid patients and deaths in the Los Angeles County area have also fallen.

COVID-19 & Stroke
- Dynamic Interactions Unfolding in Real-time

Sars-CoV-2
COVID-19

Direct Cause
2-5X Risk

Acute Stroke

Cerebrovascular Disease

Risk of Severe COVID-19

Delays in Care

~40% declines in stroke admissions worldwide

~2X Risk
COVID-19 Delays in Stroke Care

Collateral Effect of Covid-19 on Stroke Evaluation in the United States

Figure 1. Daily Counts of Unique Patients Who Underwent Neuroimaging for Stroke in the United States, July 2019 through April 2020.

All the neuroimaging tests were processed with RAPID software. Each dot represents a daily count of patients. Shaded regions correspond to the pre-pandemic (blue) and early-pandemic (yellow) epochs. The increase in the number of patients who underwent imaging from July 2019 to March 2020 reflects an increase in the number of hospitals that were using RAPID software.

Kansagra et al NEJM 2020
Time interval between last-known-well time (LKW) and arrival at the stroke center (minutes).

160 min delay in presentation due to COVID-19

Translates to 304 million neurons lost per stroke
2,955 Ischemic Stroke Patients
14 Comprehensive Stroke Centers
in 9 U.S. States
(home to 47% of all U.S. COVID-19 patients)

<table>
<thead>
<tr>
<th></th>
<th>Pre-COVID-19 (3/1/19-7/31/19)</th>
<th>COVID-19 (3/1/20-7/31/20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrival to CT</td>
<td>37min (IQR 15-101)</td>
<td>29min (IQR 14-77)**</td>
</tr>
<tr>
<td>CT to needle</td>
<td>22min (IQR 13-37)</td>
<td>29min (IQR 18-41)*</td>
</tr>
<tr>
<td>CT to thrombectomy</td>
<td>90min (IQR 73-129)</td>
<td>83min (IQR 63-133)</td>
</tr>
</tbody>
</table>

NO difference in tPA treatment rates: 14% vs. 16%
NO difference in thrombectomy rates: 61% vs. 70%
FASTER treatment times with use of Emergency Medical Services!

Treatment during COVID-19:
45% LOWER ODDS of tPA in 60min
aOR 0.55 (95%CI 0.35-0.85, p<0.01)
Overall door-to-needle 42 vs. 46 min, p=0.03
Neurologic
- Headaches
- Dizziness
- Encephalopathy
- Guillain-Barré
- Ageusia
- Myalgia
- Anosmia
- Stroke

Thromboembolism
- Deep vein thrombosis
- Pulmonary embolism
- Catheter-related thrombosis

Cardiac
- Takotsubo cardiomyopathy
- Myocardial injury/myocarditis
- Cardiac arrhythmias
- Cardiogenic shock
- Myocardial ischemia
- Acute cor pulmonale

Renal
- Acute kidney injury
- Proteinuria
- Hematuria

Endocrine
- Hyperglycemia
- Diabetic ketoacidosis

Hepatic
- Elevated aminotransferases
- Elevated bilirubin

Dermatological
- Petechiae
- Livedo reticularis
- Erythematous rash
- Urticaria
- Vesicles
- Pernio-like lesions

Gastrointestinal
- Diarrhea
- Nausea/vomiting
- Abdominal pain
- Anorexia
Tracing the path of Sars-CoV-2-related Stroke Knowledge
Rate of new neurologic events in COVID-19 infections (Jan-Mar 2020):

3.5% (32/917) overall and 9.4% (30/319) with severe or critical COVID-19.
Lombardy, Italy

High rate of co-morbid COVID-19 & stroke

COVID-19 associated with significantly worse outcomes

**Figure** Weekly admissions of patients with neurologic diseases with and without coronavirus disease 2019 (COVID-19)

<table>
<thead>
<tr>
<th>Admitting neurologic diagnosis, n (%)</th>
<th>0.035</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular disease</td>
<td></td>
</tr>
<tr>
<td>111 (64.2)</td>
<td>68 (58.1)</td>
</tr>
<tr>
<td>43 (76.8)</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td></td>
</tr>
<tr>
<td>23 (13.3)</td>
<td>19 (16.2)</td>
</tr>
<tr>
<td>4 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Inflammatory/infectious disease</td>
<td></td>
</tr>
<tr>
<td>9 (5.2)</td>
<td>9 (7.7)</td>
</tr>
<tr>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Neoplastic</td>
<td></td>
</tr>
<tr>
<td>3 (1.7)</td>
<td>3 (2.6)</td>
</tr>
<tr>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>27 (15.6)</td>
<td>18 (15.4)</td>
</tr>
<tr>
<td>9 (16.1)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>In hospital mortality, n (%)</td>
<td></td>
</tr>
<tr>
<td>19 (17.1)</td>
<td>4 (5.0)</td>
</tr>
<tr>
<td>15 (34.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mRS score discharge</td>
<td></td>
</tr>
<tr>
<td>2.0 (1.0–5.0)</td>
<td>2.0 (1.0–3.0)</td>
</tr>
<tr>
<td>5.0 (2.0–6.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Good outcome</td>
<td></td>
</tr>
<tr>
<td>59 (53.2)</td>
<td>48 (70.6)</td>
</tr>
<tr>
<td>11 (25.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
United Kingdom

Coronerve Study Group
- Neurologic events related to COVID-19
- Case reporting map

@NeuroCov on Twitter

Figure 4: Age distribution of patients identified through the CoroNerve surveillance study meeting the clinical case definitions for cerebrovascular and neuropsychiatric events
8.4% rate of stroke among hospitalized COVID-19 patients

7.6X the rate of stroke in patients admitted with influenza
Evidence mounts
- Recent excellent meta-analysis
- Disturbing trends:
  - 1.8% risk (2x ↑ than Sars-CoV1, 8X ↑ than flu)
  - High mortality 45%
  - Half of COVID-19-related strokes in young occur in absence of COVID-19 symptoms
More than 20,000 patients hospitalized with COVID-19 across the U.S. between January and November 2020

Two hundred eighty-one people (1.4%) in the COVID-19 CVD Registry had a stroke confirmed by diagnostic imaging during hospitalization.
- 148 patients (52.7%) experienced ischemic stroke;
- 7 patients (2.5%) had transient ischemic attack (TIA)
- 127 patients (45.2%) experienced a bleeding stroke or unspecified type of stroke

- More likely male and older (mean age 65)
- More likely African-American
- Ischemic stroke patients more likely to have DM2 and HTN than those without stroke
- In-hospital death rate 2X (37% vs. 16%)

Emmons-Bell et al. Circulation 202
Reciprocal Interaction?

A History of Cerebrovascular Disease Worsens COVID-19 Outcomes

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cerebrovascular Dis (+)</th>
<th>Cerebrovascular Dis (-)</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bai T 2020</td>
<td>2</td>
<td>7</td>
<td>34</td>
</tr>
<tr>
<td>Cao J 2020</td>
<td>3</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Chen T 2020</td>
<td>4</td>
<td>4</td>
<td>109</td>
</tr>
<tr>
<td>Luo XM 2020</td>
<td>22</td>
<td>39</td>
<td>78</td>
</tr>
<tr>
<td>Yuan M 2020</td>
<td>1</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>32</td>
<td>244</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>32</td>
<td>244</td>
<td>1084</td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.09; Chi² = 3.15; df = 4 (P = 0.53); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 7.81 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Severe COVID-19

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cerebrovascular Dis (+)</th>
<th>Cerebrovascular Dis (-)</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Guan 2020</td>
<td>4</td>
<td>15</td>
<td>169</td>
</tr>
<tr>
<td>Hu L 2020</td>
<td>3</td>
<td>7</td>
<td>169</td>
</tr>
<tr>
<td>Qin 2020</td>
<td>8</td>
<td>11</td>
<td>278</td>
</tr>
<tr>
<td>Wang Dan 2020</td>
<td>3</td>
<td>5</td>
<td>68</td>
</tr>
<tr>
<td>Wang Y 2020</td>
<td>3</td>
<td>7</td>
<td>35</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>34</td>
<td>787</td>
<td>138</td>
</tr>
<tr>
<td>Total events</td>
<td>34</td>
<td>787</td>
<td>138</td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.59; Chi² = 44.70; df = 6 (P &lt; 0.00001); I² = 87%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.96 (P = 0.05)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 119 3402 100.0% 2.04 [1.43, 2.91]

Total events 66 1031

Heterogeneity: Tau² = 0.27; Chi² = 48.38; df = 11 (P < 0.00001); I² = 77%
Test for overall effect: Z = 3.95 (P < 0.00001)
Test for subarachnoid differences: Chi² = 0.50, df = 1 (P = 0.48), I² = 0%
COVID-19 Neuro Network of Brain Infections Global
https://braininfectionsglobal.tghn.org/covid-neuro-network/

Ellul et al. Lancet Neurol 2020
A week in the life: UCLA COVID-19 related strokes

- 43 yo F with atypical clot in the internal carotid artery
- Aortic thrombus with LVO
- Total carotid occlusion
- Brainstem infarct
- IVH
- Massive CVT
Management of COVID-19-related Stroke

1st Challenge: Diagnosis and Workflow

Ospel and Goyal Nature Rev Neurol 2020
Management of COVID-19-related Stroke

2nd Challenge: Thrombolysis

Stroke Care during the COVID-19 Pandemic: International Expert Panel Review

"Safety is brain" over “time is brain”

IV Thrombolysis recommended but with precautions for providers and expectation of worse outcomes

Venketasubramanian et al. Cerebrovasc Dis 2020

Zhou et al. JNNP 2021
Management of COVID-19-related Stroke

3rd Challenge: Medication Management for Secondary Prevention

Table 1. Characteristics of the Included Articles

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Type of article</th>
<th>Age (years)/sex</th>
<th>Secondary prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yaghi et al, 2020</td>
<td>USA</td>
<td>Case Series</td>
<td>40, 40, 50, 50, 50; sex: NR</td>
<td>Anticoagulant</td>
</tr>
<tr>
<td>Oxley et al, 2020</td>
<td>USA</td>
<td>Case series</td>
<td>33/F; 37/M</td>
<td>Apixaban 5 mg twice daily</td>
</tr>
<tr>
<td>Fara et al, 2020</td>
<td>USA</td>
<td>Case series</td>
<td>33/F</td>
<td>Aspirin plus clopidogrel then switched to apixaban 5 mg twice daily</td>
</tr>
<tr>
<td>Ashrafi et al, 2020</td>
<td>Iran</td>
<td>Case series</td>
<td>33/F; 39/M; 40/M</td>
<td>Aspirin plus clopidogrel</td>
</tr>
<tr>
<td>Deliwala et al, 2020</td>
<td>USA</td>
<td>Case report</td>
<td>31/F</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Reddy et al, 2020</td>
<td>USA</td>
<td>Case series</td>
<td>47/M; 39/F</td>
<td>Antiplatelet</td>
</tr>
<tr>
<td>Franceschi et al, 2020</td>
<td>USA</td>
<td>Case series</td>
<td>33/M; 37/F</td>
<td>Anticoagulant (one of them received argatroban)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>16 patients</td>
<td>Anticoagulant: 10; dual antiplatelet: 3; single antiplatelet: 3</td>
</tr>
</tbody>
</table>

M: male; F: female; NR: not reported.
COVID-19 Vaccine Related Cerebrovascular Disease

- December 11: BNT162b2 EUA Approved
- December 18: mRNA-1273 EUA Approved
- January 29: ChAdOx1 nCov-19 CMA Approved
- February 27: Ad26.COV2.5 EUA Approved
- April 7: EMA announces link between ChAdOx1 nCov-19 and VITT
- April 13: FDA/CDC announce pause on Ad26.COV2.5 use following 6 cases of CVT
- April 23: FDA/CDC resume Ad26.COV2.5 use
- May 5: ChAdOx1 nCov-19 CVT incidence estimated at 2.5 per 100,000

Daily Worldwide COVID-19 Deaths

- December 2020
- January 2021
- February
- March
- April
- May

Vaccine Use

- BNT162b2
- mRNA-1273
- ChAdOx1 nCov-19
- Ad26.COV2.5
Influenza Vaccination as a Stroke Prevention Tool

• Vaccination doesn’t just prevent infection, but also reduces stroke risk

COVID-19 Vaccine Related Cerebrovascular Disease

Schulz et al. Ann Neurol 2021
COVID-19 vs. Vaccine-related Cerebral Venous Thrombosis

Siegler et al. Stroke 2021
Diagnosis and Management of COVID-19 Vaccine Related CVT

Suspect VITT

- **Platelets <150,000 μl**
- **Adenovirus-based Vaccine Exposure within 28 days**
- **OR**
  - CVT
  - Multiple VTE

Diagnose VITT

- MRV or CTV
- Anti-PF4 Antibody ELISA
- Rule Out Other Causes

Treatment

- IV Ig (1g/kg x 2 days)
- Non-Heparin Anticoagulation
- Refractory to Management
- Endovascular Venous Clot Retrieval

Long Term

- Direct Oral Anticoagulation or Vitamin K Antagonist for Minimum 3 Months

 Patients

- ChAdOx1 nCov-19 Recipients
- Ad26.COV2.S Recipients
- COVID-19 Infected Patients

Diagnose

- CVT

1 in 40,000

1 in 470,000

1 in 5,000 to 15,000

Siegler et al. Stroke 2021
WHAT THE FUTURE HOLDS

A steady return to pre-pandemic stroke volumes
- But with sicker patients

Dynamic stroke care provided in real-time via video interfaces

Flexible stroke center workflows to accommodate unexpected emergencies

Improved recognition of the contribution of viruses and inflammation to stroke cause (and improved vaccination rates!)

Identification of factors driving intrinsic susceptibility to stroke

A roaring 20s of stroke research that will lead to new treatments and preventive strategies