Stroke and Covid-19

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Case

- 33 F with 1 week of cough, headache and chills

- Progressive dysarthria with both numbness in the left arm and leg over 28 hours
- **Delayed ED care due to fear of Covid**
- NIHSS at presentation 19
- CT small RMCA stroke, CTA partially occlusive thrombus in the RMCA, R Carotid bifurcation.
- CT chest- patchy ground glass opacities – SARS- COV2 +
- Anticoagulation
- Repeat CTA in 10 days- resolution of thrombus
COVID-19 CASES

To rapidly communicate information on the global clinical effort against Covid-19, the Journal has initiated a series of case reports that offer important teaching points or novel findings. The case reports should be viewed as observations rather than as recommendations for evaluation or treatment. In the interest of timeliness, these reports are evaluated by in-house editors, with peer review reserved for key points as needed.

Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young
The start of the connection..!

• 5 patients younger than 50 yrs admitted for large vessel occlusion ischemic stroke during the height of the pandemic in NY in a 2 week period (March 23rd to April 7th, 2020).

• All tested + for SARS- CoV2

• No vascular risk factors.

• 7 fold increase in LVO in younger age group compared to previous year.

• Labs showed hypercoagulable state.

• Postulated that stroke related to presence of SARS-CoV2 in these patients.
Table 1. Clinical Characteristics of Five Young Patients Presenting with Large-Vessel Stroke.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>33</td>
<td>37</td>
<td>39</td>
<td>44</td>
<td>49</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Medical history and risk factors for stroke†</td>
<td>None</td>
<td>None</td>
<td>Hyperlipidemia, hypertension</td>
<td>Undiagnosed diabetes</td>
<td>Mild stroke, diabetes</td>
</tr>
<tr>
<td>Medications</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Aspirin (81 mg), atorvastatin (80 mg)</td>
</tr>
<tr>
<td>NIHSS score‡</td>
<td>19</td>
<td>13</td>
<td>16</td>
<td>23</td>
<td>13</td>
</tr>
<tr>
<td>On admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 24 hr</td>
<td>17</td>
<td>11</td>
<td>4</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>At last follow-up</td>
<td>13</td>
<td>5</td>
<td>NA; intubated and sedated, with multorgan failure</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>(on day 14)</td>
<td></td>
<td>(on day 10)</td>
<td></td>
<td>(on day 12)</td>
<td>(on day 4)</td>
</tr>
<tr>
<td>Outcome status</td>
<td>Discharged to rehabilitation facility</td>
<td>Discharged to rehabilitation facility</td>
<td>Intensive care unit</td>
<td>Stroke unit</td>
<td>Discharged to rehabilitation facility</td>
</tr>
<tr>
<td>Time to presentation — hr</td>
<td>28</td>
<td>16</td>
<td>8</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Signs and symptoms of stroke</td>
<td>Hemiplegia on left side, facial droop, gaze paresis, hemihemianopia, dysarthria, sensory deficits</td>
<td>Reduced level of consciousness, dysarthria, hemiplegia on right side, dysarthria, sensory deficits</td>
<td>Reduced level of consciousness, hemiplegia on right side, gaze paresis</td>
<td>Reduced level of consciousness, hemiplegia on left side, dysarthria, facial weakness</td>
<td>Reduced level of consciousness, hemiplegia on left side, dysarthria, sensory deficits</td>
</tr>
<tr>
<td>Vascular territory</td>
<td>Right internal carotid artery</td>
<td>Left middle cerebral artery</td>
<td>Right posterior cerebral artery</td>
<td>Left middle cerebral artery</td>
<td>Right middle cerebral artery</td>
</tr>
<tr>
<td>Imaging for diagnosis</td>
<td>CT, CTA, CTP, MRI</td>
<td>CT, CTA, CTP, MRI</td>
<td>CT, CTA, CTP, MRI</td>
<td>CT, CTA, CTP</td>
<td>CT, CTA, CTP</td>
</tr>
<tr>
<td>Treatment for stroke</td>
<td>Apixaban (5 mg twice daily)</td>
<td>Clot retrieval, apixaban (5 mg twice daily)</td>
<td>Clot retrieval, aspirin (81 mg daily)</td>
<td>Intravenous t-PA, clot retrieval, hemiendarterectomy, aspirin (81 mg daily)</td>
<td>Clot retrieval, stent, aspirin (325 mg daily), clopidogrel (75 mg daily)</td>
</tr>
<tr>
<td>Covid-19 symptoms</td>
<td>Cough, headache, chills</td>
<td>No symptoms; recently exposed to family member with PCR-positive Covid-19</td>
<td>None</td>
<td>None</td>
<td>Lethargy</td>
</tr>
<tr>
<td>White-cell count — per mm³</td>
<td>7800</td>
<td>9900</td>
<td>5500</td>
<td>9000</td>
<td>4900</td>
</tr>
<tr>
<td>Platelet count — per mm³</td>
<td>427,000</td>
<td>299,000</td>
<td>135,000</td>
<td>372,000</td>
<td>255,000</td>
</tr>
<tr>
<td>Prothrombin time — sec</td>
<td>13.3</td>
<td>13.4</td>
<td>14.4</td>
<td>12.8</td>
<td>15.2</td>
</tr>
<tr>
<td>Activated partial-thromboplastin time — sec</td>
<td>25.0</td>
<td>42.7</td>
<td>27.7</td>
<td>26.9</td>
<td>37.0</td>
</tr>
<tr>
<td>Fibrinogen — mg/dl</td>
<td>501</td>
<td>370</td>
<td>739</td>
<td>443</td>
<td>531</td>
</tr>
<tr>
<td>d-dimer — ng/ml</td>
<td>460</td>
<td>52</td>
<td>2230</td>
<td>13,800</td>
<td>1750</td>
</tr>
<tr>
<td>Ferritin — ng/ml</td>
<td>7</td>
<td>136</td>
<td>1564</td>
<td>987</td>
<td>596</td>
</tr>
</tbody>
</table>

* Reference ranges are as follows: platelet count, 150,000 to 450,000 per cubic millimeter; prothrombin time, 12.3 to 14.9 seconds; activated partial-thromboplastin time, 25.4 to 34.9 seconds; fibrinogen, 126 to 450 mg per deciliter; d-dimer, 0 to 500 ng per milliliter; and ferritin, 30 to 400 ng per milliliter. CT denotes computed tomography, CTA CT angiography, CTP CT perfusion, MRI magnetic resonance imaging. NA not applicable, PCR polymerase chain reaction, and t-PA tissue plasminogen activator.
† The patients were screened for smoking, hypertension, hyperlipidemia, diabetes, atrial fibrillation, congestive heart failure, illicit drug use, and neck trauma.
‡ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher numbers indicating more severe stroke.
Facts

• SARS-CoV-2 more likely to cause thrombotic vascular events including stroke compared to other coronavirus strains and seasonal infectious diseases.

• 7.6% increase in the odds of stroke compared to influenza virus.

• Reported incidence of stroke in Covid 19 patients -> 1-6% ( per LANCET Sept 1,2020)

• WHO panel review- Risk of ischemic stroke during COVID-19 – 5%

• Higher frequency of ischemic stroke in young subjects with COVID-19, no vascular risk factors – raises possibility of mechanisms peculiar to COVID-19 may be responsible.
Facts

• Ischemic stroke more common than Hemorrhagic stroke (few cases reported)

• Median time from diagnosis to ischemic stroke-10 days (per small study)

• Hemorrhagic stroke related to venous sinus thrombosis has been reported with COVIS-19 viral infection.

• Majority cryptogenic, directly associated with COVID-19
Recent study – Emory GA

• 396 ischemic stroke patients, 13 diagnosed with COVID-19 (March to July 2020).

• Stroke more common in patients with risk factors like DM, HTN, HLD, Afib/flutter.

• Males and African Americans primary affected

• Prevalence of cryptogenic stroke

69% in COVID-19 ischemic stroke and 17% in Non COVID-19 ischemic strokes.

(Usually cryptogenic stroke account for 10-30% of ischemic stroke)
Proposed mechanisms

• Hypercoagulable state from systemic inflammation and cytokine storm.

• Postinfectious immune mediated responses

• Direct viral-induced endotheliitis or endotheliopathy, potentially leading to angiopathic thrombosis, with viral particles having been isolated from the endothelium of various tissue, including brain tissue

• Cardiomyopathy
Hypercoagulable state

- 20-55% patients with COVID-19 – lab evidence of coagulopathy

Increased level of D-dimer, prolongation of PTT, mild thrombocytopenia and decreased fibrinogen level (in late disease)

- Lupus anticoagulant reported to be + in 45% patient with COVID-19 - study

- International Society of Thrombosis and Hemostasis

Monitor PTT, D-Dimer, Platelet count and fibrinogen and prophylactic LMWH in all patients with COVID-19

- Postmortem studies in COVID-19 patients- microvascular platelet fibrin rich thrombotic depositions in lungs and other organs including brain.
Hypercoagulable state

• 10 patients with stroke and COVID-19 – large artery occlusions in multiple vascular territories suggesting mechanism to cardioembolic / paradoxical – study

• German study: Recent autopsy in 12 patients – fresh thrombus in 7 patients

• French study- 79% of 34 patients had DVT within 48 hrs after admission.

• Findings suggest paradoxical emboli could be the plausible mechanism in some patient with COVID-19 coagulopathy.

• Paradoxical emboli – large artery ischemic stroke in young, extracranial (Common and internal carotid occlusions)
Vasculitis

• SARS-CoV-2 – affinity to ACE2 receptors (lungs, heart, kidney, small bowel) – COVID 19 clinical presentation

• ACE2 receptors- abundant in vascular endothelium- inflammatory response “lymphocytic endothelitis”

• Vessel inflammation
  1. Direct local effect of SARS-CoV-2 on ACE2 receptors
  2. Systemic immune response to the virus- “Cytokine storm”

• More data needed regarding angiographic and postmortem studies of cervical- cerebral vasculature- to evaluate presence of vasculitis/potential role in in-situ clot formation

• Elevated inflammatory markers- CRP, Ferritin

• Large vessel occlusions in atypical locations- extensive thrombus in the common carotid artery
Cardiomyopathy

Number of mechanisms of cardiac involvement

1. Direct invasion (affinity to ACE2) causing myocarditis

2. Indirect systemic inflammation - cytokine storm

3. Increased cardiac stress due to respiratory failure /hypoxemia - stress cardiomyopathy.

4. Stimulation of sympathetic nervous system → stress cardiomyopathy & cardiac arrhythmia → intracardiac thrombus (+ hypercoagulable state) → cardio embolic stroke.
MRI brain/ Imaging findings/CSF

- Leptomeningeal enhancement (62%)
- Perfusion abnormalities 11/11 (100%)
- Cerebral ischemic stroke 3/13 (23%)

- CSF
  OG band 2/7 (29%)
  Elevated CSF IgG and CSF protein levels (1/7)
  Negative RT-PCR for SARS-COV-2 in CSF 7/7 (100%)
MRI Shows Brain Abnormalities in Some COVID-19 Patients

59 yo intubated with AMS
Post GAD images with bilateral leptomeningeal enhancement
Hemorrhagic stroke from venous thrombosis

MRI, venous CT scanner, and cerebral angiography at admission and day 14. MRI images (a, b) demonstrates voluminous left temporal hemorrhage with venous thrombosis (arrow). Venous CT scanner (c–f) confirms the existence of the extensive venous thrombosis. Located in the straight sinus and left lateral sinus (arrow). Day 14 CT scanner shows contro-lateral. Brain hemorrhage (g) and cerebral angiography shows persistent left thrombosis (h).
Therapy Implications

Anticoagulation

- Suspected cardioembolic mechanism – multiple vascular territories, cardiomyopathy with significant ventricular dyskinesia, Afib, R→L shunt- Therapeutic dose of anticoagulation. (International Journal of stroke)
- Warfarin (targets multiple clotting factors) might be more effective than DOACs (targets one clotting factor)
- Further evidence needed from large studies

Anti-inflammatory Therapies

- Monoclonal antibodies (Tocilizumab), IL-B antagonists- potentially beneficial for COVID-19 main concern- delay in elimination of virus, secondary infection (study)
- Corticosteroids – empirically used for COVID-19 complications of ARDS, acute cardiac and renal involvement.
- Role of anti-inflammatory agents and Corticosteroids in stroke – debatable.

Antivirals

- Remdesivir – no role reported in stroke
Neurologic Complications of COVID-19

• Viral meningitis
• Anosmia
• Encephalitis
• Post-infectious acute disseminated encephalomyelitis
• Post-infectious brainstem encephalitis
• Guillain-Barre syndrome
• Myositis
• Acute necrotizing hemorrhagic encephalopathy
Acute Hemorrhagic necrotizing Encephalopathy

- Bilateral thalamic swelling
- Punctate hemorrhagic foci on SWI
Nationwide observations

• Decreased incidence of mild stroke- likely secondary to quarantine effect

• Nationwide analysis – decreasing imaging evaluation of stroke during the pandemic.
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 prepandemic (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.
Screening and Diagnosis of COVID-19

• Screen all patients presenting with acute stroke for COVID-19 adhering to local ED/EMS protocols

• Until confirmed, assume all patients presenting with acute stroke are COVID-19 positive. Utilize appropriate PPE and prevention strategies to keep staff safe

• When indicated, utilize low-dose chest CT at the same time as head CT/CTA to support in diagnosis of COVID-19
Limit exposure and Conserve PPE

• Limit excessive use of PPE and potential exposure to healthcare workers:

• Utilize virtual means if they will suffice (virtual or remote stroke assessment)

• Limit the number of people in attendance at acute stroke codes

• Go straight to angio suite when able

• Wait on any tests that won't change immediate management while COVID results pending
Protected CODE STROKE (PCS)

**Screening Prior to Code Stroke**

- On Pre-notification
  - Is the patient exhibiting any infectious symptoms (infection Control Screen)?
  - Fever, cough, chest pain, dyspnea, headache, myalgias, anemia/GI symptoms
  - Does the patient or a close contact have a travel history?
  - ANY of the above are POSITIVE? → proceed as a PCS

- Historical and Examination Features
  - NO or POSITIVE Infection Control Screen?
  - Unclear history? Patient unable to communicate?
  - Decreased level of consciousness? presyncope/syncope?
  - History or examination features suggestive of an alternate (non-stroke) diagnosis?
    - ANY of the above are TRUE? → proceed as a PCS

**Protected Code Stroke**

- Use Personal Protective Equipment (PPE) and Place a Mask on the Patient
  - (1) Use Droplet/Contact PPE: full-sleeved gown, surgical mask, eye protection and gloves (ideal to use extended cuff gloves)
  - Is there Aerosalization? e.g. oropharyngeal/nasal (open) suctioning, intubation, non-invasive ventilation, Code Blue and/or CPR
    - Aerosalization? → use Airborne/Droplet/Contact PPE: full-sleeved gown, N95 mask, eye protection and gloves (ideal to use extended cuff gloves)
  - (2) Place a surgical mask on the non-intubated patient (after securing your own PPE)
    - Mask should stay on the patient during transport to and from imaging
  - Is the patient obtunded? Needing high FIO₂ (> 0.5)? Needing CPAP, BiPAP, Nasal High Flow therapy, or Bag-Valve-Mask ventilation?
    - YES to ANY → Consider EARLY intubation, Consult ED/ICU physician for airway management prior to transport to imaging

- (3) Use Crisis Resource Management
  - Do Not Rush inside the resuscitation room, “slow-down when you should”
  - Designate a Safety Leader to monitor PPE donning/doffing
  - Role designate your team and avoid crowding (ideally perform a pre-brief)
  - Ensure PPE is donned by all team members before starting PCS
  - Avoid Contamination of other hospital environments en-route to imaging and back

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**Patient from the field (EMS/direct to ED)**
- Infection Control Screen POSITIVE and/or Travel History POSITIVE

**Patient transferred from another facility WITHOUT:**
- Infection Control Screen and/or Travel History Screening

**Unclear/Unable to provide History, ANY Historical/Exam features suggestive of alternate diagnosis**

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Physician Discretion and Clinical Judgement

Protected Code Stroke
Some Things Don’t change..!

• Stroke is still a medical emergency. Call 911. !
• Delayed medical care can lead to permanent disabling symptoms which could have been reversible if timely action was taken.!

**B E F A S T**

**BALANCE**
Loss of balance, headache or dizziness

**EYES**
Blurred vision

**FACE**
One side of the face is drooping

**ARMS**
Arm or leg weakness

**SPEECH**
Speech difficulty

**TIME**
Time to call for ambulance immediately
Community education

• Keep your preventative health appointments

• Stay Healthy, avoid infection, take precautions, wear a mask.

• Find ways to stay active
  • Take walks outside
  • Create a space for fitness, mindfulness/meditation at home

• Managing loneliness and isolation. Stay connected with friends and family
  • Have virtual visits

• Pay attention to your emotional and mental wellbeing.

• If something isn’t right, come in right away

• Get your flu shot!
Take home points

• Stroke has been seen as the presenting symptoms in some patients with Covid 19. There is a proposed connection.

• Ischemic stroke is more common than hemorrhagic stroke.

• Most ischemic stroke are cryptogenic with underlying COVID-19 infection.

• Hypercoagulability, vasculitis, cardiomyopathy are the proposed mechanisms.

• Can affect young without risk factors and old with risk factors.

• Anticoagulation with Heparin/Warfarin might be more effective in treatment than DOAC’s. Further evidence needed from larger studies.

• Multiple small studies and case series. Large multi center trials underway.

• DO NOT ignore your stroke symptoms..!! Call 911.
Since the beginning of the pandemic, have you seen more younger patient without risk factors presenting with stroke at your facility?

- Yes
- No
Have you seen a decline in number of patients or delayed presentation after symptoms onset in your respective facilities?

Yes

No
THANK YOU
References

1. Mechanisms of Stroke in COVID-19
   Spence J.D.\textsuperscript{a} · de Freitas G.R.\textsuperscript{b} · Pettigrew L.C.\textsuperscript{c} · Ay H.\textsuperscript{d} · Liebeskind D.S.\textsuperscript{e} · Kase C.S.\textsuperscript{f} · Del Brutto O.H.\textsuperscript{g} · Hankey G.J.\textsuperscript{h} · Venketasubramanian N.\textsuperscript{i}

2. COVID-19 related stroke in young individuals
   https://doi.org/10.1016/S1474-4422(20)30272-6

3. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young


5. Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs Patients With Influenza
   Alexander E. Merkler, MD\textsuperscript{1}; Neal S. Parikh, MD, MS\textsuperscript{1}; Saad Mir, MD\textsuperscript{1}; et al
   https://jamanetwork.com/journals/jamaneurology/fullarticle/2768098