NEUROLOGIC MANIFESTATIONS OF SARS-COV-2 (COVID-19) INFECTION

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DISCLOSURES

- Dr. Karanjia has provided expert witness testimony
- Dr. Karanjia has been compensated for consultation by ThirdBridge and M3 consultants regarding neurocritical care management of status epilepticus, thermoregulatory management, and andexanet alfa.
NEUROLOGIC MANIFESTATIONS OF VIRAL INFECTIONS

- Direct infection
  - CNS
    - **Meningitis/encephalitis** (incidence 1/200K/yr) (esp. HSV, VZV, WNV/arbovirus, enterov., Chikungunya, flu, SARS-CoV1, CoV2) -> encephalopathy, cerebral edema, high ICP, seizure, focal neuro deficit, headache
    - Vasculitis/vessel inflammation (HIV, VZV, CMV, WNV, HCV, probably CoV2) -> large/small vessel stroke, venous/cavernous sinus thrombosis, encephalopathy
    - **Acute flaccid paralysis/myelitis** (polio, enterovirus, WNV) -> limb weakness, cranial nerve dysfunction, respiratory failure 2/2 respiratory muscle
  - PNS (HIV, HTLV, HSV, VZV, CMV, EBV, WNV, HCV, rabies)
    - Direct invasion: cranial/motor/sensory neuropathy -> motor/sensory deficit in peripheral nerve distribution, autonomic instability
    - Radiculitis -> motor/sensory deficit in radicular distribution

Bold=most common
NEUROLOGIC MANIFESTATIONS OF VIRAL INFECTIONS

- **Parainfectious/autoimmune**
  - **CNS**
    - ADEM (Acute Disseminated Encephalomyelitis)/Acute Necrotizing Encephalopathy (ANE) - cerebral edema, encephalopathy, focal neuro deficit, seizure
    - (Influenza, hepatitis, HHV6, EBV, CMV, HIV, Zika, Dengue, CoV2)
    - Transverse myelitis (spinal cord) - tetra/paraplegia, sensory level
    - (HSV, VZV, CMV, EBV, WNV, Zika, influenza, echo, Hep B, mumps, measles, rubella)
  - **PNS**
    - Guillain-Barre (EBV, CMV, Zika, influenza, CoV2) - acute ascending paralysis/cranial neuropathy (hrs/days), autonomic instability
    - AIDP (acute inflammatory demyelinating polyneuropathy) - subacute ascending paralysis (wks)
      - influenza, coxsackie, EBV, CMV, Zika, HIV, VZV, hep B, rubella, measles)
  - **Myocarditis** (adenovirus, enterovirus, parvovirus, CoV2)
    - Arterial strokes
  - **Hypercoagulable state** (EBV, HSV, CMV, anything causing SIRS/DIC, including influenza, SARS CoV1 and CoV2)
    - Arterial strokes, venous/cavernous sinus thrombosis
  - **Hypocoagulable state** (hemorrhagic fever viruses, viruses causing DIC e.g. rotavirus, VZV, rubella, rubeola, influenza)
    - Intracerebral, subarachnoid, subdural hemorrhage
  - **Byproduct of critical illness** (anything that lands you in the ICU, including CoV2)
    - Critical illness polyneuropathy/myopathy, seizure, delirium

**Bold=most common**
WHAT WE KNOW ABOUT SARS-COV-2 (COVID-19) NEURO COMPLICATIONS SO FAR

Currently reported neurologic complications of critically ill COVID-19 patients:

- Meningitis/encephalitis
- Seizures/status epilepticus
- Encephalopathy/delirium (up to 69%)
- Ischemic stroke (up to 23%)
- Venous sinus thrombosis
- Acute Disseminated Encephalomyelitis/Acute Necrotizing Encephalopathy
- Guillain-Barre
- Intracerebral hemorrhage (related to anticoagulation for ECMO)
- Intraventricular hemorrhage with resultant hydrocephalus (related to anticoagulation for ECMO)
- Subarachnoid hemorrhage (related to anticoagulation for ECMO)
- 8/22 pts who died from COVID-19 had SARS-CoV2 in brain tissue on autopsy
POSSIBLE PATHOGENESIS

- 2 typical routes of viral spread to CNS:
  - Hematogenous: infect endothelial BBB cells/infected leukocytes that migrate through BBB
  - Neuronal dissemination: infect peripheral neurons -> retrograde transport into CNS

- Animal models/human in vitro studies of coronaviruses including SARS-CoV1/MERS demonstrate direct CNS invasion through both routes

- SARS-CoV-1 and CoV-2 found in human brain tissue on autopsy

- LPs of SARS-CoV-1 and CoV-2 pts w/ neuro sx have viral RNA in CSF

- Early anosmia without congestion in SARS-CoV-2 is unique. May mean neuro invasion through olfactory bulb occurs early.

- Brain MRI in COVID-19 pt w/ anosmia demonstrates likely viral invasion of the brain through olfactory bulb

- Endothelial cell infection demonstrated in human renal, lung, heart, small bowel on autopsy
WHAT WE KNOW ABOUT SARS-COV-2 (COVID-19) NEURO COMPLICATIONS SO FAR

- Wuhan, China
- 214 hospitalized patients with lab confirmed SARS-CoV2
- Avg. age 52, 59% female, 39% w/ underlying HTN, DM, CAD, CA
- 78 (36.4%) had neurologic manifestations
- More severe COVID illness=more likely to have neuro sxes (46% of severe/mech vent vs 30% nonsevere/non-mech vent). p<0.05
- Acute stroke 5.7% (severe COVID) vs .1% (nonsevere COVID); 2.8% overall
- Impaired consciousness 14.8% vs 2.4%
- Skeletal muscle injury 19.3 % vs 4.8%
- Dizziness 17% vs 15%
- Headache 13% vs 10%
- Loss of taste 5.6%, loss of smell 5%
- In severe pts w/ CNS sxes: WBC, plt counts lower (1 vs 1.2; 180 vs 227) and BUN higher (4.5 vs 4.1)
WHAT WE KNOW ABOUT SARS-COV-2 (COVID-19) NEURO COMPLICATIONS SO FAR

- Strasbourg, France
- 58 hospitalized patients with lab-confirmed SARS-CoV-2, mean age 63
- Neuro findings recorded in 8 pts on ICU admit, 39 w/ sedation held
- Agitation present in 69% when paralytic d/c’d
- 26/40 (65%) CAM-ICU +
- 67% had diffuse corticospinal tract signs (increased reflexes)
- 15/45 (33%) discharged pts had dysexecutive syndrome (inattention, disorientation, poorly organized movements)
- MRI done in 13 pts
  - Leptomeningeal enhancement 8/13
  - Bilateral frontotemporal hypoperfusion in 11/11 patients
  - 3/13 (23%) patients with (small) ischemic strokes
- LP done in 7 pts
  - Cells: none
  - Nonspecific changes (oligoclonal bands, elevated protein) in 3
  - SARS-CoV-2 PCR negative in all pts
- EEG done in 8 pts
  - All w/ nonspecific changes. 1/8 had diffuse bifrontal slowing

Neurologic Features in Severe SARS-CoV-2 Infection

TO THE EDITOR: We report the neurologic features in an observational series of 58 of 64 consecutive patients admitted to the hospital because of acute respiratory distress syndrome (ARDS) due to Covid-19. The patients received similar evaluations by intensivists in two intensive care units (ICUs) in Strasbourg, France, between March 3 and April 3, 2020.

Six patients were excluded because of paralytic neuromuscular blockade when neurologic data were collected or because they had died without a neurologic examination having been performed. In all 58 patients, reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays of nasopharyngeal samples were positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The median age of the patients was 65 years, and the median Simplified Acute Physiology Score II at the time of neurologic examination was 52 (interquartile range, 37 to 65, on a scale ranging from 0 to 165, with higher scores indicating greater severity of illness). Seven patients had had previous neurologic disorders including transient ischemic attack, partial epilepsy, and mild cognitive impairment.

The neurologic findings were recorded in 8 of the 58 patients (14%) on admission to the ICU (before treatment) and in 39 patients (67%) when sedation and a neuromuscular blocker were withdrawn. Agitation was present in 40 patients (69%) when neuromuscular blockade was withdrawn (Supplementary Table 1). A total of 26 of 40 patients were noted to have confusion according to the Confusion Assessment Method for the ICU; those patients could be evaluated when they were responsive.

Table 1. Characteristics of the Patients with Covid-19 and ARDS.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (N=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation for ARDS</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>50 (86)</td>
</tr>
<tr>
<td>No. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>Days of treatment</td>
<td>4</td>
</tr>
<tr>
<td>Median</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>4–7</td>
</tr>
<tr>
<td>Propofol</td>
<td>27 (47)</td>
</tr>
<tr>
<td>No. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>Days of treatment</td>
<td>0†</td>
</tr>
<tr>
<td>Median</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>1–6</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>58 (100)</td>
</tr>
<tr>
<td>No. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>Days of treatment</td>
<td>4</td>
</tr>
<tr>
<td>Median</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>4–12</td>
</tr>
<tr>
<td>Neurologic signs — no./total no. (%)</td>
<td>49/58 (84)</td>
</tr>
<tr>
<td>Temperature &gt;38.5°C on day of clinical examination</td>
<td>8/49 (16)</td>
</tr>
<tr>
<td>Positive findings on CAM-ICU</td>
<td>26/40 (65)</td>
</tr>
<tr>
<td>Agitation</td>
<td>40/58 (69)</td>
</tr>
<tr>
<td>Corticospinal tract signs</td>
<td>39/58 (67)</td>
</tr>
<tr>
<td>Dysexecutive syndrome</td>
<td>14/59 (26)</td>
</tr>
<tr>
<td>Brain MRI — no./total no. (%)</td>
<td></td>
</tr>
<tr>
<td>Leptomeningeal enhancement</td>
<td>8/13 (62)</td>
</tr>
<tr>
<td>Perfusion abnormalities</td>
<td>11/11 (100)</td>
</tr>
<tr>
<td>Cerebral ischemic stroke</td>
<td>3/13 (23)</td>
</tr>
<tr>
<td>CSF analysis — no./total no. (%)</td>
<td></td>
</tr>
<tr>
<td>Oligoclonal bands in serum</td>
<td>2/7 (29)</td>
</tr>
<tr>
<td>Elevated CSF IgG and IgM</td>
<td>1/7 (14)</td>
</tr>
<tr>
<td>Low albumin level</td>
<td>4/7 (57)</td>
</tr>
<tr>
<td>Negative RT-PCR for SARS-CoV-2 in CSF</td>
<td>7/7 (100)</td>
</tr>
</tbody>
</table>

ARDS denotes acute respiratory distress syndrome. CSF, cerebrospinal fluid. MRI, magnetic resonance imaging. RT-PCR, reverse-transcriptase polymerase chain.
Wuhan, China

99 patients hospitalized w/lab confirmed SARS-Cov-2

Mean age 55, 51% w/chronic diseases

8% headache

9% confusion

WHAT WE KNOW ABOUT SARS-COV-2 (COVID-19) NEURO COMPLICATIONS SO FAR

- Age
  - Mean (SD): 55.5 (13.1)
  - Range: 21-82
  - <39: 10 (10.0%)
  - 40-49: 22 (22.2%)
  - 50-59: 30 (30.3%)
  - 60-69: 22 (22.2%)
  - ≥70: 15 (15.1%)
- Sex
  - Female: 32 (32.3%)
  - Male: 67 (68.8%)
- Occupation
  - Agricultural worker: 2 (2.0%)
  - Self-employed: 65 (65.6%)
  - Employee: 35 (35.3%)
  - Retired: 39 (39.4%)
- Exposure to Huanan seafood market*
  - 49 (49.5%)
- Family history of psychiatric disorders
  - 37 (37.4%)
- Admission to intensive care unit
  - 23 (23.2%)

Clinical outcome

- Remained in hospital
  - 57 (58.6%)
- Discharged
  - 31 (31.3%)
- Died
  - 11 (11.1%)

Data are n (%) unless specified otherwise. *2019-nCoV-2019 novel coronavirus.

Table 1: Demographics, baseline characteristics, and clinical outcomes of 99 patients admitted to Wuhan Jinyintan Hospital (Jan 1–20, 2020) with 2019-nCoV pneumonia

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WHAT WE KNOW ABOUT SARS-COV-2 (COVID-19) NEURO COMPLICATIONS SO FAR

- Northern Italy
- 5/1000-1200 (0.5%) admitted patients w/ SARS-CoV-2 infection with Guillain-Barre
- 4/5 BLE weakness/paresthesias
- 1/5 facial diplegia->ataxia paresthesia
- Flaccid quadriparesis within 36h-4d
- 1st CoV sx -> 1st GBS sx 5-10 days
- 3/5 required mechanical ventilation
- No patients w/ dysautonomia
- EMG: axonal variant GBS in 3/5, demyelinating GBS in 2/5
- MRI: nerve root enhancement 3/5
- CSF: no cells, SARS-CoV-2 PCR negative
- All pts rx'd w/ IVIG, 2 received 2nd course, 1 started PLEX
- 4 wks after, 2/5 in ICU on vent, 2 getting PT for flaccid quadriplegia, 1 able to walk independently
WHAT WE KNOW ABOUT COVID-19 NEUROCOMPLICATIONS SO FAR

- The Netherlands, 3 hospitals
- 184 hospitalized ICU-level lab confirmed SARS-CoV-2 patients, average age 64
- All received standard thromboprophylaxis
- 31% had thrombotic complications (symptomatic acute PE, CVT, MI, ischemic stroke, systemic arterial embolus)
- 3/184 (3.7%) had ischemic strokes diagnosed on CT

Table 1
Characteristics of included patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean, standard deviation)</td>
<td>64 (12)</td>
</tr>
<tr>
<td>Male sex (number, %)</td>
<td>139 (76)</td>
</tr>
<tr>
<td>Body weight (mean, standard deviation)</td>
<td>87 (16)</td>
</tr>
<tr>
<td>Active cancer (number, %)</td>
<td>5 (27)</td>
</tr>
<tr>
<td>Coagulopathy during admission a (n, %)</td>
<td>70 (38)</td>
</tr>
<tr>
<td>Therapeutic anticoagulation at admission (n, %)</td>
<td>17 (9.2)</td>
</tr>
<tr>
<td>Renal replacement therapy during admission (n, %)</td>
<td>23 (13%)</td>
</tr>
</tbody>
</table>

a Defined as: spontaneous prolongation of the prothrombin time (PT) > 3.5 or

Table 2
Local protocol for thromboprophylaxis in participating centres for patients admitted to the intensive care unit during the study period.

<table>
<thead>
<tr>
<th>Site</th>
<th>Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leiden University Medical Center</td>
<td>Nadroparin 2850 IU sc per day or 5700 IU per day if body weight &lt; 100 kg</td>
</tr>
<tr>
<td>Erasmus University Medical Center</td>
<td>Nadroparin 5700 IU per day; nadroparin 5700 IU sc twice daily from April 4th 2020 and onwards</td>
</tr>
<tr>
<td>Amphia Hospital Brede</td>
<td>Nadroparin 2850 IU sc per day or 5700 IU per day if body weight &gt; 100 kg</td>
</tr>
<tr>
<td></td>
<td>Nadroparin 5700 IU sc per day from March 30th 2020 and onwards</td>
</tr>
</tbody>
</table>

Note: acute pulmonary embolism was diagnosed with CT-pulmonary angiography, deep vein thrombosis/upper extremity vein thrombosis was diagnosed with ultrasonography, strokes were diagnosed with CT.
ANECTDOTAL EVIDENCE

- Increased risk of stroke in young minimally symptomatic patients with no CV risk factors:
  - Mt. Sinai: Young, minimally symptomatic COVID-19 patients are experiencing large vessel strokes at rates much higher (7x) than anticipated for that age group. COVID-19 stroke pts are 15 yrs younger than average stroke pts
  - Thomas Jefferson Univ. Hospitals: 12 COVID pts with LVO stroke over 3 wks, 40% under 50yo

- Reports of seizures/status epilepticus
  - 1 Report of ADEM
  - 1 Report of ANE
  - Cases of IVH, ICH, SAH in patients on V-V ECMO on standard ECMO anticoagulation
**TREATMENTS**

- **Direct CNS infection:** supportive, standard neuro-ICU care
  - Seizures -> antiepileptics. If altered > 15 minutes after seizure, or has no known reason for AMS, eEG to rule out nonconvulsive seizures
  - Cerebral edema/increased ICP -> HOB up, Na checks q6h, set sodium goal, normocarbia, sedate/reduce cerebral electrical activity, consider normothermia and surgery for focal lesions. If prone, reverse Trendelenburg. If cannot prone due to ICP, try chest weights for pulmonary recruitment. Consider early CRRT (BUN~60) if significant cerebral edema

- **Parainfectious**
  - ADEM/ANE -> steroids, IVIG, plasmapheresis
  - Transverse myelitis -> steroids, IVIG, plasmapheresis
  - Guillain-Barre -> IVIG, plasmapheresis

- **Secondary complications**
  - Stroke -> immediate tPA (up to 4.5h)/thrombectomy (up to 24h). Permissive HTN, cerebral perfusion/oxygenation optimization (mild hypervolemia, optimize CO, Hgb 10, normocarbia)

- **On ECMO?**
  - Diagnostics available: CTH (not MRI), EEG, TCD
  - High ICP? Treat as above. When appropriate, EVD’s and cranis have been done for non-COVID ECMO IVH/ICH/stroke patients, with some anecdotal success
  - Heparin has been held on COVID ECMO patients for days without known thrombotic complications
  - General NCC care
  - Glucose <180, no dextrose containing fluids, minimize unnecessary sedation, frequent neurochecks
PRAGMATIC NEURO TIPS FOR COVID-19 PATIENTS—FOR NOW

- Anosmia, stroke, encephalopathy, and myopathy seem to be the most common neuro manifestations of COVID-19 so far.
- In the ICU, order neurochecks at least q4h if pt is not chemically paralyzed; coordinate exams w/ nursing to save PPE.
- Minimize sedation to obtain best neuro exam as frequently as is safe while balancing risk of delirium.
- Talk to your neuro consultants before ordering off-unit neuro tests/scans.

- Focal deficit?
  - **Within 24h CALL STROKE CODE**, after 24h consult stroke team.
  - Consider CTH / MRI brain +/- contrast, + MRA head and neck.
- Encephalopathy/AMS?
  - Ddx: meningoencephalitis, arterial/venous stroke/thrombosis, nonconv. sz, high ICP, delirium, ADEM/ANE.
  - Consider CT, MRI brain +/- contrast, LP, neuro consult.
- Twitching?
  - Ddx seizure, status epilepticus, myopathy. Get stat EEG/treat empirically/consider neuro consult.
- Generalized limb weakness?
  - Ddx: critical illness polyneuropathy/myopathy, Guillain-Barre, AIDP. Could it be transverse myelitis?
- Unable to wean from vent?
  - Could it be 2/2 CNS (brainstem) or PNS (respiratory muscle) involvement?
QUESTIONS

- What is the true prevalence of all these COVID-19 neurologic complications? (meningoencephalitis? nonconvulsive seizure? stroke?)

- How do we prognosticate on a post cardiac arrest patient that might also have COVID-related CNS disease?

- How many COVID-19 pts have CNS/PNS involvement as source of respiratory failure?

- What is the prognosis of patients with COVID-19 neurologic complications?

- …?
THIS WILL CONTINUE TO EVOLVE, SO KEEP READING…
THANK YOU

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CJ Frieben

Arthur Lam
Rebecca Dodd-Sullivan
Ana Kukulj
Fernando Mediano
Sarah Norton
Khristina Vibal-Poaster
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