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

June 2, 2020

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DISCLOSURES

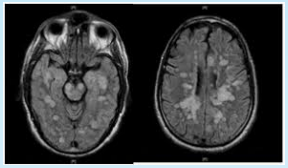
- Dr. Karanjia has provided expert witness testimony
- Dr. Karanjia has been compensated for consultation by ThirdBridge and M3 consultants regarding neurocritical care management of status epilepticus, thermoregulatory management, and andexanet alfa.

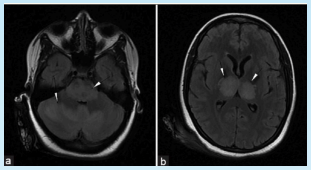
NEUROLOGIC MANIFESTATIONS OF VIRAL INFECTIONS

- 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





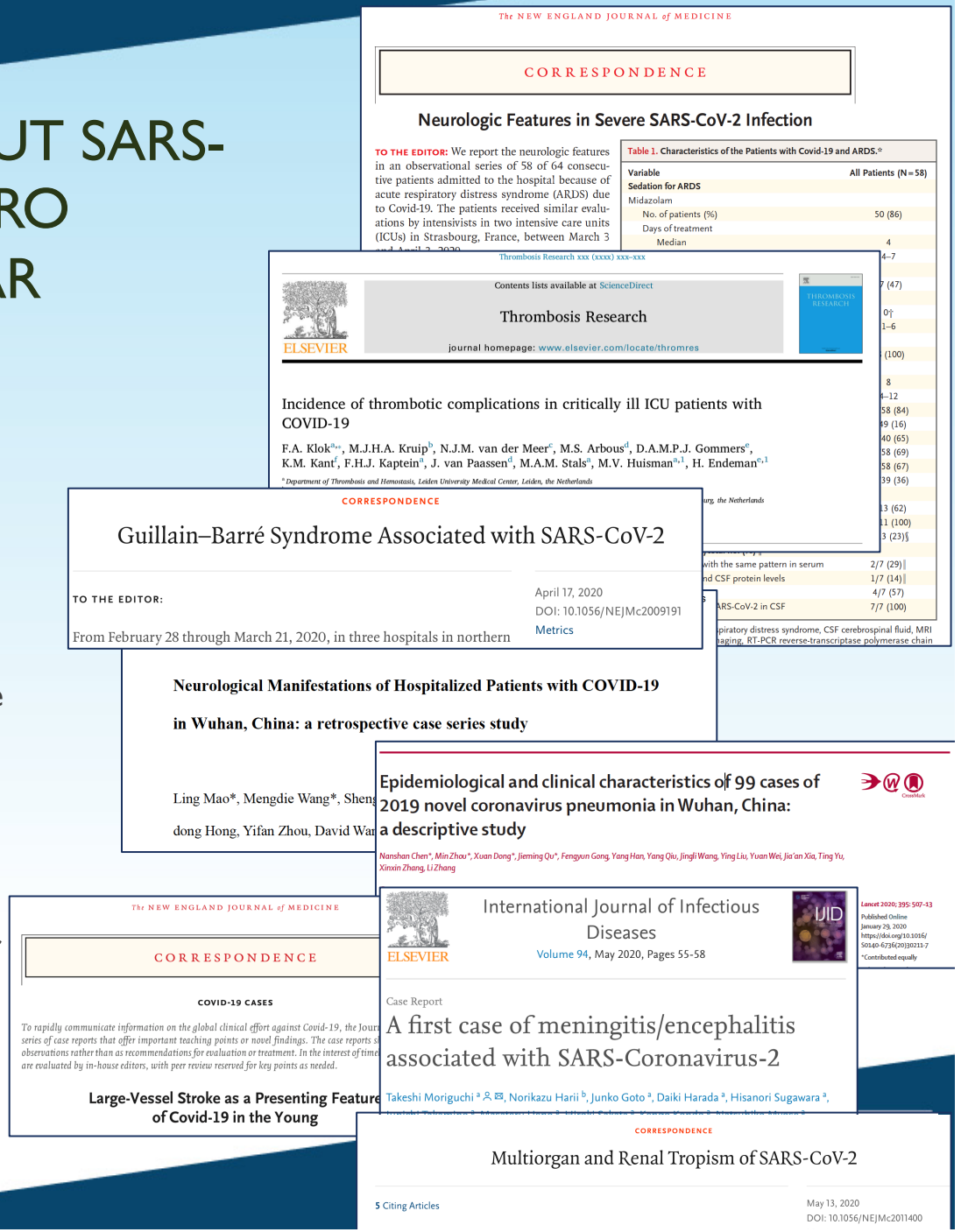
- Parainfectious/autoimmune
  - CNS
    - ADEM (Acute Disseminated Encephalomyelitis)/Acute Necrotizing Encephalopathy (ANE)-> cerebral edema, encephalopathy, (Influenza, hepatitis, HHV6, EBV, CMV, HIV, Zika, Dengue, CoV2) focal neuro deficit, seizure
    - Transverse myelitis (spinal cord) -> tetra/paraplegia, sensory level (HSV, VZV, CMV, EBV, WNV, Zika, influenza, echo, Hep B, mumps, measles, rubella) autonomic instability, incontinence
  - PNS
    - **Guillain-Barre** (EBV, CMV, Zika, influenza, CoV2) -> acute ascending paralysis/cranial neuropathy(hrs/days), autonomic instability
    - AIDP (acute inflamm. 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
- Enecphalopathy/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 SARSCoV2 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 sxs 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**

Human coronavirus: respiratory pathogens revisited as infectious neuroinvasive, neurotropic, and neurovirulent agents

February 2013

In book: Neuroviral infections : RNA viruses and retroviruses (pp.93-122) · Chapter: CHAPTER 5 : HUMAN CORONAVIRUSES: RESPIRATORY PATHOGENS REVISITED AS INFECTIOUS NEUROINVASIVE, NEUROTROPIC AND NEUROVIRULENT AGENTS · Publisher: CRC press · Editors: Sunit K. Singh, Daniel Ruzek

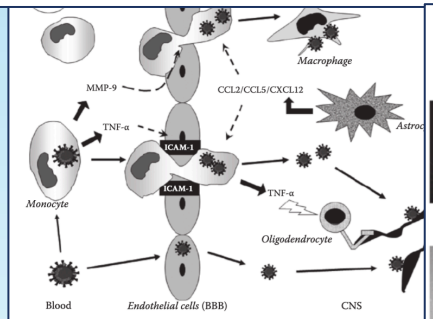


figure 5.2 Hematogenous route of neuroinvasion and possible mechanism of neu lence of HCoV. Human monocytes are susceptible to infection by HCoVs includin CoV and are activated after infection. This activation involves, among other fa production of MMP-9, which increases the permeability of the BBB, and of TNF- up-regulates the adhesion molecule ICAM-1 on endothelial cells of the BBB, fa the passage of infected monocytes into the central nervous system (CNS). Viruses directly infect endothelial cells to gain access to the CNS, where they can infect Once in the CNS, the infected and activated monocytes such as TNF-α that can damage the myelin-synthesizin Infected monocyte-derived macrophages that entered t chemokines, such as CCL5, CXCL10, or CXCL11, whic and/or other monocytes into the CNS. These cells may pathogenesis after infection. Moreover, after sensing th chemokines, such as CCL2, CCL5, and CXCL12, that w of more infected leukocytes. Thus, coronaviruses can ini

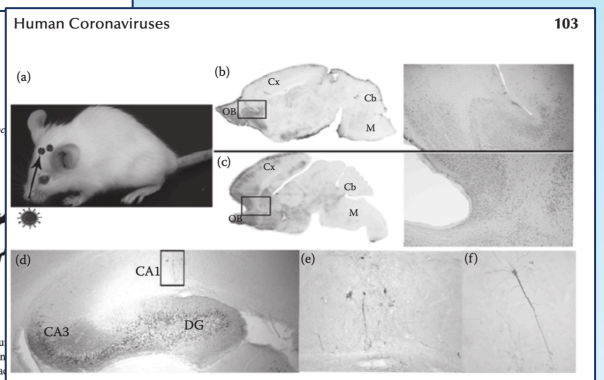


figure 5.3 Transneuronal route of neuroinvasion through the olfactory nerve and spread into the CNS of HCoV. (a) After intranasal infection of susceptible mice, HCoV-OC43 is

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REVIEW

JOURNAL OF MEDICAL VIROLOGY WI

The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients

Yan-Chao Li[1] | Wan-Zhu Bai[2] | Tsutomu Hashikawa[3]

New Online Views 45,661 | Citations 0 | Altmetri

Images in Neurology

May 29, 2020

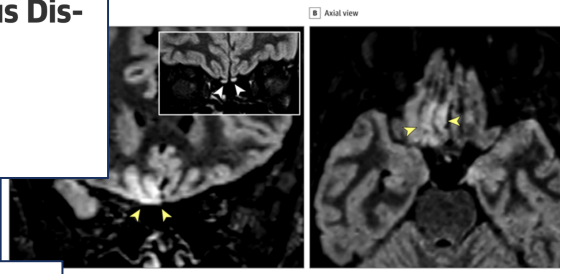
Magnetic Resonance Imaging Alteration of the Brain in a Patient With Coronavirus Disease 2019 (COVID-19) and Anosmia

Letterio S. Politi, MD[1,2,3]; Ettore Salsano, MD[4]; Marco Grimaldi, MD[1]

» Author Affiliations | Article Information

JAMA Neurol. Published online May 29, 2020. doi:10.1001/jamaneurol.2020.2125

agnetic Resonance Imaging Alterations in a Patient With Coronavirus D-19) Presenting With Anosmia 4 Days From Symptom Onset



and axial (B) reformatted 3-dimensional fluid-attenuated inversion recovery (FLAIR) imag

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CORRESPONDENCE | VOLUME 395, ISSUE 10234, P1417-1418, MAY 02, 2020

PDF [409 KB] Figures Sav

Endothelial cell infection and endotheliitis in COVID-19

Zsuzsanna Varga · Andreas J Flammer · Peter Steiger · Martina Haberecker · Rea Andermatt · Annelies S Zinkernagel · et al. Show all authors

Published: April 20, 2020 · DOI: https://doi.org/10.1016/S0140-6736(20)30937-5

Endothelial cell infection and endotheliitis in COVID-19

Cardiovascular complications are rapidly emerging as a key threat in coronavirus disease 2019 (COVID-19) in addition to respiratory disease. The mechanisms underlying the disproportionate effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on patients with cardiovascular comorbidities, however, remain incompletely

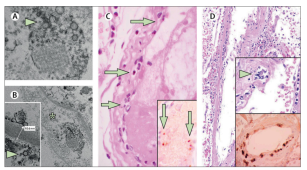

Figure: Pathology of endothelial cell dysfunction in COVID-19
(A, B) Electron microscopy of kidney tissue shows viral inclusion bodies in a peritubular space and viral

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 sxs (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 sxs: WBC, plt counts lower (1 vs 1.2; 180 vs 227) and BUN higher (4.5 vs 4.1)

Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: a retrospective case series study

Ling Mao*, Mengdie Wang*, Shengcai Chen*, Quanwei He*, Jiang Chang*, Candong Hong, Yifan Zhou, David Wang, Yanan Li†, Huijuan Jin†, Bo Hu†

Table 1 Clinical characteristics of patients with COVID-19

	Total (n=214)	Severe (n=88)	Non-severe (n=126)	*P*
Age (y), means ± standard deviations	52.7±15.5	58.2±15.0	48.9±14.7	
Age, n (%)				<0.001
<50 y	90 (42.1)	24 (27.3)	66 (52.4)	
≥50 y	124 (57.9)	64 (72.7)	60 (47.6)	
Sex, n (%)				<0.05
Female	127 (59.3)	44 (50.0)	83 (65.9)	
Male	87 (40.7)	44 (50.0)	43 (34.1)	
Comorbidities, n (%)				
Any	83 (38.8)	42 (47.7)	41 (32.5)	<0.05
Hypertension	51 (23.8)	32 (36.4)	19 (15.1)	<0.001
Diabetes	30 (14.0)	15 (17.0)	15 (11.9)	0.287
Cardio cerebrovascular disease	15 (7.0)	7 (8.0)	8 (6.3)	0.651
Malignancy	13 (6.1)	5 (5.7)	8 (6.3)	0.841
Chronic kidney disease	6 (2.8)	2 (2.3)	4 (3.2)	0.694
Typical symptoms, n (%)				
Fever	132 (61.7)	40 (45.5)	92 (73.0)	<0.001
Dry cough	107 (50.0)	30 (34.1)	77 (61.1)	<0.001
Anorexia	68 (31.8)	21 (23.9)	47 (37.3)	<0.05
Diarrhea	41 (19.2)	13 (14.8)	28 (22.2)	0.1730
Pharyngalgia	31 (14.5)	10 (11.4)	21 (16.7)	0.278
Abdominal pain	10 (4.7)	6 (6.8)	4 (3.2)	0.214
Nervous system symptoms, n (%)				
Any	78 (36.4)	40 (45.5)	38 (30.2)	<0.05
CNS	53 (24.8)	27 (30.7)	26 (20.6)	0.094
Dizziness	36 (16.8)	17 (19.3)	19 (15.1)	0.415
Headache	28 (13.1)	15 (17.0)	13 (10.3)	0.151
Impaired consciousness	16 (7.5)	13 (14.8)	3 (2.4)	<0.001
Acute cerebrovascular disease	6 (2.8)	5 (5.7)	1 (0.8)	<0.05
Ataxia	1 (0.5)	1 (1.1)	0 (0.0)	NA
Epilepsy	1 (0.5)	1 (1.1)	0 (0.0)	NA
PNS	19 (8.9)	7 (8.0)	12 (9.5)	0.691
Hypogeusia	12 (5.6)	3 (3.4)	9 (7.1)	0.243
Hyposmia	11 (5.1)	3 (3.4)	8 (6.3)	0.338
Hypopsia	3 (1.4)	2 (2.3)	1 (0.8)	0.365
Neuralgia	5 (2.3)	4 (4.5)	1 (0.8)	0.074
Muscle injury	23 (10.7)	17 (19.3)	6 (4.8)	<0.001

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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 dysexecute 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

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

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 63 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 163, 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.

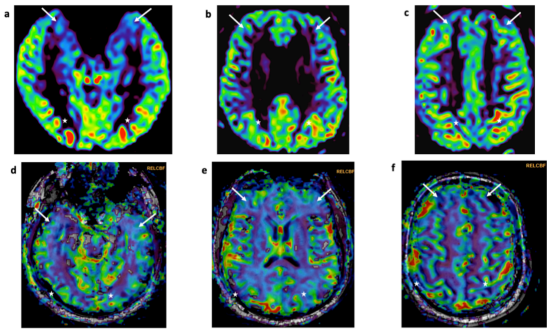
The neurologic findings were recorded in 8 of the 58 patients (14%) on admission to the ICU (before treatment) and in 39 patients (67%) when sedation and a neuromuscular blocker were withheld. Agitation was present in 40 patients (69%) when neuromuscular blockade was discontinued (Table 1). A total of 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.*

Variable	All Patients (N=58)
Sedation for ARDS	
Midazolam	
No. of patients (%)	50 (86)
Days of treatment	
Median	4
Interquartile range	4–7
Propofol	
No. of patients (%)	27 (47)
Days of treatment	
Median	0†
Interquartile range	1–6
Sufentanil	
No. of patients (%)	58 (100)
Days of treatment	
Median	8
Interquartile range	4–12
Neurologic signs — no./total no. (%)	49/58 (84)
Temperature >38.5°C at time of clinical examination	8/49 (16)
Positive findings on CAM-ICU‡	26/40 (65)
Agitation	40/58 (69)
Corticospinal tract signs	39/58 (67)
Dysexecutive syndrome	14/39 (36)
Brain MRI — no./total no. (%)	
Leptomeningeal enhancement	8/13 (62)
Perfusion abnormalities	11/11 (100)
Cerebral ischemic stroke	3/13 (23)§
CSF analysis — no./total no. (%)¶	
Oligoclonal bands with the same pattern in serum	2/7 (29)‖
Elevated CSF IgG and CSF protein levels	1/7 (14)‖
Low albumin level	4/7 (57)
Negative RT-PCR for SARS-CoV-2 in CSF	7/7 (100)

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

Supplementary figure 2:



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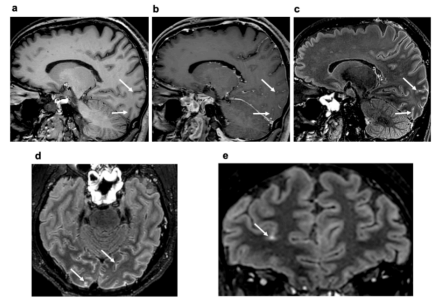

WHAT WE KNOW ABOUT SARS-COV-2 (COVID-19) NEURO COMPLICATIONS SO FAR

- Wuhan, China
- 99 patients hospitalized w/ lab confirmed SARS-Cov-2
- Mean age 55, 51% w/ chronic diseases
- 8% headache
- 9% confusion

Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study

Nanshan Chen, Min Zhou*, Xuan Dong*, Jieming Qu*, Fengyun Gong, Yang Han, Yang Qiu, Jingli Wang, Ying Liu, Yuan Wei, Jia'an Xia, Ting Yu, Xinxin Zhang, Li Zhang*

Summary

Background In December, 2019, a pneumonia associated with the 2019 novel coronavirus (2019-nCoV) emerged in Wuhan, China. We aimed to further clarify the epidemiological and clinical characteristics of 2019-nCoV pneumonia.

Methods In this retrospective, single-centre study, we included all confirmed cases of 2019-nCoV in Wuhan Jinyintan Hospital from Jan 1 to Jan 20, 2020. Cases were confirmed by real-time RT-PCR and were analysed for epidemiological, demographic, clinical, and radiological features and laboratory data. Outcomes were followed up until Jan 25, 2020.

Lancet 2020; 395: 507–13

Published Online January 29, 2020 https://doi.org/10.1016/S0140-6736(20)30211-7

*Contributed equally

	Patients (n=99)
Age, years	
Mean (SD)	55·5 (13·1)
Range	21–82
≤39	10 (10%)
40–49	22 (22%)
50–59	30 (30%)
60–69	22 (22%)
≥70	15 (15%)
Sex	
Female	32 (32%)
Male	67 (68%)
Occupation	
Agricultural worker	2 (2%)
Self-employed	63 (64%)
Employee	15 (15%)
Retired	19 (19%)
Exposure to Huanan seafood market*	49 (49%)
Long-term exposure history	47 (47%)
Short-term exposure history	2 (2%)
Chronic medical illness	50 (51%)
Cardiovascular and cerebrovascular diseases	40 (40%)
Digestive system disease	11 (11%)
Endocrine system disease†	13 (13%)
Malignant tumour	1 (1%)
Nervous system disease	1 (1%)
Respiratory system disease	1 (1%)
Admission to intensive care unit	23 (23%)
Clinical outcome	
Remained in hospital	57 (58%)
Discharged	31 (31%)
Died	11 (11%)

Data are n (%) unless specified otherwise. 2019-nCoV=2019 novel coronavirus. *Long-term exposure is having worked at or lived in or around Huanan seafood market, whereas short-term exposure is having been to Huanan seafood market occasionally. †12 were diabetic.

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

	Patients (n=99)
Signs and symptoms at admission	
Fever	82 (83%)
Cough	81 (82%)
Shortness of breath	31 (31%)
Muscle ache	11 (11%)
Confusion	9 (9%)
Headache	8 (8%)
Sore throat	5 (5%)
Rhinorrhoea	4 (4%)
Chest pain	2 (2%)
Diarrhoea	2 (2%)
Nausea and vomiting	1 (1%)
More than one sign or symptom	89 (90%)
Fever, cough, and shortness of breath	15 (15%)
Comorbid conditions	
Any	33 (33%)
ARDS	17 (17%)
Acute renal injury	3 (3%)
Acute respiratory injury	8 (8%)
Septic shock	4 (4%)
Ventilator-associated pneumonia	1 (1%)
Chest x-ray and CT findings	
Unilateral pneumonia	25 (25%)
Bilateral pneumonia	74 (75%)
Multiple mottling and ground-glass opacity	14 (14%)
Treatment	
Oxygen therapy	75 (76%)
Mechanical ventilation	
Non-invasive (ie, face mask)	13 (13%)
Invasive	4 (4%)
CRRT	9 (9%)
ECMO	3 (3%)
Antibiotic treatment	70 (71%)
Antifungal treatment	15 (15%)
Antiviral treatment	75 (76%)
Glucocorticoids	19 (19%)
Intravenous immunoglobulin therapy	27 (27%)

2019-nCoV=2019 novel coronavirus. ARDS=acute respiratory distress syndrome. ECMO=extracorporeal membrane oxygenation. CRRT=continuous renal replacement therapy.

Table 2: **Clinical characteristics and treatment of patients with 2019-nCoV pneumonia**

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 sxs -> 1st GBS sxs 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

CORRESPONDENCE

Guillain–Barré Syndrome Associated with SARS-CoV-2

TO THE EDITOR:

From February 28 through March 21, 2020, in three hospitals in northern

April 17, 2020
DOI: 10.1056/NEJMc2009191
Metrics

Table 1. Characteristics of Five Patients with Guillain–Barré Syndrome after the Onset of Covid-19.*

Patient No.	Onset of Neurologic Syndrome	Neurologic Signs and Symptoms	CSF Findings†	Antiganglioside Antibodies‡	MRI Results	Treatment and Outcomes at Week 4
1	7 Days after fever, cough, and ageusia	Flaccid areflexic tetraplegia evolving to facial weakness, upper-limb paresthesia (36 hr), and respiratory failure (day 6)	Day 2 (first lumbar puncture): normal protein level; no cells; negative PCR assay for SARS-CoV-2 Day 10 (second lumbar puncture): protein level, 101 mg/dl; white-cell count, 4 per mm³; negative PCR assay for SARS-CoV-2	Negative	Head: normal Spine: enhancement of caudal nerve roots	Received 2 cycles of IVIG; had poor outcomes, including persistence of severe upper-limb weakness, dysphagia, and lower-limb paraplegia
2	10 Days after fever and pharyngitis	Facial diplegia and generalized areflexia evolving to lower-limb paresthesia with ataxia (day 2)	Day 3: protein level, 123 mg/dl; no cells; negative PCR assay for SARS-CoV-2	Not tested	Head: enhancement of facial nerve bilaterally Spine: normal	Received IVIG; had improvements, including decrease in ataxia and mild decrease in facial weakness
3	10 Days after fever and cough	Flaccid tetraparesis and facial weakness evolving to areflexia (day 2) and respiratory failure (day 5)	Day 3: protein level, 193 mg/dl; no cells; negative PCR assay for SARS-CoV-2	Negative	Head: normal Spine: enhancement of caudal nerve roots	Received 2 cycles of IVIG; had poor outcomes, including ICU admission owing to neuromuscular respiratory failure and flaccid tetraplegia
4	5 Days after cough and hyposmia	Flaccid areflexic tetraparesis and ataxia (day 4)	Day 5: normal protein level; no cells; negative PCR assay for SARS-CoV-2	Not tested	Head: normal Spine: normal	Received IVIG; had mild improvement but unable to stand 1 mo after onset
5	7 Days after cough, ageusia, and anosmia	Facial weakness, flaccid areflexic paraplegia (days 2–3), and respiratory failure (day 4)	Day 3: protein level, 40 mg/dl; white-cell count, 3 per mm³; CSF:serum albumin ratio, 1.2%; negative PCR assay for SARS-CoV-2	Negative	Head: not performed Spine: normal	Received IVIG and plasma exchange; had bacterial pneumonia during IVIG treatment, which delayed plasma exchange

* Covid-19 denotes coronavirus disease 2019, CSF cerebrospinal fluid, ICU intensive care unit, IVIG intravenous immune globulin, MRI magnetic resonance imaging, PCR polymerase chain reaction, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.
† On CSF analysis, all the patients had a normal glucose level and IgG index and a polyclonal pattern on electrophoresis. The normal range for the protein level is 15 to 45 mg per deciliter.
‡ An enzyme-linked immunosorbent assay was used to test for antibodies to GM1, GQ1b, and GD1b.

WHAT WE KNOW ABOUT COVID-19 NEURO COMPLICATIONS 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**

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Incidence of thrombotic complications in critically ill ICU patients with COVID-19

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Thromboprophylaxis

ABSTRACT

Introduction: COVID-19 may predispose to both venous and arterial thromboembolism due to excessive inflammation, hypoxia, immobilisation and diffuse intravascular coagulation. Reports on the incidence of thrombotic complications are however not available.

Methods: We evaluated the incidence of the composite outcome of symptomatic acute pulmonary embolism (PE), deep-vein thrombosis, ischemic stroke, myocardial infarction or systemic arterial embolism in all COVID-19 patients admitted to the ICU of 2 Dutch university hospitals and 1 Dutch teaching hospital.

Results: We studied 184 ICU patients with proven COVID-19 pneumonia of whom 23 died (13%), 22 were discharged alive (12%) and 139 (76%) were still on the ICU on April 5th 2020. All patients received at least standard doses thromboprophylaxis. The cumulative incidence of the composite outcome was 31% (95%CI 20-41), of which CTPA and/or ultrasonography confirmed VTE in 27% (95%CI 17-37%) and arterial thrombotic events in 3.7% (95%CI 0-8.2%). PE was the most frequent thrombotic complication (n = 25, 81%). Age (adjusted hazard ratio (aHR) 1.05/per year, 95%CI 1.004-1.01) and coagulopathy, defined as spontaneous prolongation of the prothrombin time > 3 s or activated partial thromboplastin time > 5 s (aHR 4.1, 95%CI 1.9-9.1), were independent predictors of thrombotic complications.

Conclusion: The 31% incidence of thrombotic complications in ICU patients with COVID-19 infections is remarkably high. Our findings reinforce the recommendation to strictly apply pharmacological thrombosis prophylaxis in all COVID-19 patients admitted to the ICU, and are strongly suggestive of increasing the prophylaxis towards high-prophylactic doses, even in the absence of randomized evidence.

Table 1
Characteristics of included patients.

Age (Mean, standard deviation)	64 (12)
Male sex (number, %)	139 (76)
Body weight (mean, standard deviation)	87 (16)
Active cancer (number, %)	5 (2.7)
Coagulopathy during admission[a] (n, %)	70 (38)
Therapeutic anticoagulation at admission (n, %)	17 (9.2)
Renal replacement therapy during admission (n, %)	23 (13%)

[a] Defined as: spontaneous prolongation of the prothrombin time (PT) >3 s or

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

Site	
Leiden University Medical Center	nadroparin 2850 IU sc per day or 5700 IU per day if body weight > 100 kg
Erasmus University Medical Center	Nadroparin 5700 IU per day; nadroparin 5700 IU sc twice daily from April 4th 2020 and onwards
Amphia Hospital Breda	Nadroparin 2850 IU sc per day or 5700 IU per day if body weight > 100 kg; nadroparin 5700 IU sc per day from March 30th 2020 and onwards

Table 3
Description of thrombotic complications.

Type of event	Number of cases	Relevant d
Pulmonary embolism	25	– 18 cases with at least PE in segmental arteries, 7 cases PE limited to subsegmental arteries
Other venous thromboembolic events	3	– 1 proximal deep-vein thrombosis of the leg – 2 catheter related upper extremity thrombosis
Arterial thrombotic events	3	– All ischemic strokes

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.

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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

The Washington Post

Young, healthy people barely sick with covid-19 are dying from strokes

Ariana Eunjung Cha 2 days ago

News > Medscape Medical News > Neurology News

COVID-19 Linked to Large Vessel Stroke in Young Adults

Damian McNamara
April 24, 2020

20 Read Comments Share ADD TO EMAIL ALERTS

Editor's note: Find the latest COVID-19 news and guidance in Medscape's Coronavirus Resource Center.

Physicians in New York City, which still leads the nation in reported COVID-19 cases, are reporting significantly more acute, large vessel strokes in young adults infected with COVID-19.

In a rapid communication to be published online April 29 in the *New England Journal of Medicine*, investigators led by Thomas Oxley, MD, PhD, department of neurosurgery, Mount Sinai Health System, report five cases of large vessel stroke over a 2-week period in COVID-19 patients under age 50 years. This represents a sevenfold increase in what would normally be expected.

The five cases had either no, or mild, COVID-19 symptoms.

1

COVID-19-Associated Acute Disseminated Encephalomyelitis – A Case Report

Tianshu Zhang, M.D., Michael B. Rodricks, M.D., Ellen Hirsh, M.D.

Robert Wood Johnson University Hospital Somerset, 110 Rehill Ave., Somerville, NJ 08876

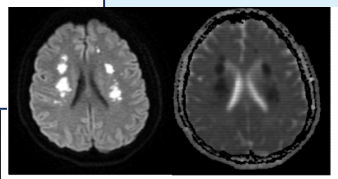


Fig. 2 MRI brain - subcortical diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) map changes

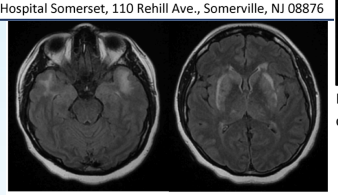


Fig. 3 MRI brain - subcortical and temporal T2 FLAIR changes

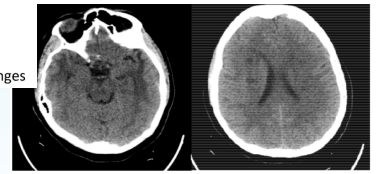


Fig. 1 CT head - bilateral temporal and subcortical hypodensity

Clin Neurophysiol. 2020 May 13 PMCID: PMC7217773
doi: 10.1016/j.clinph.2020.05.005 [Epub ahead of print] PMID: 32405258

Non-lesional status epilepticus in a patient with coronavirus disease 2019

Gaëlle Balloy,[a,*] Pierre-Joachim Mahé,[b] Laurène Leclair-Visonneau,[a,c] Yann Péréon,[a] Pascal Derkinderen,[c,d] Armelle Magot,[a] and Arnaud Peyre[a]

Author information · Article notes · Copyright and License information Disclaimer

Some Coronavirus Patients Show Signs of Brain Ailments

Doctors have observed neurological symptoms, including confusion, stroke and seizures, in a small subset of Covid-19 patients.

A coronavirus patient being transferred from a full hospital in Brussels, Belgium, on Wednesday. Francisco Seco/Associated Press

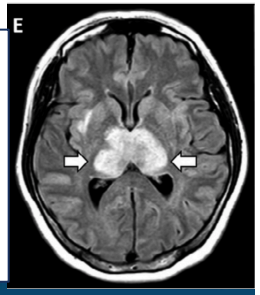
Reviews and Commentary Free Access
Images in *Radiology*

COVID-19–associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features

Neo Poyiadji, Gassan Shahin, Daniel Noujaim, Michael Stone, Suresh Patel, Brent Griffith

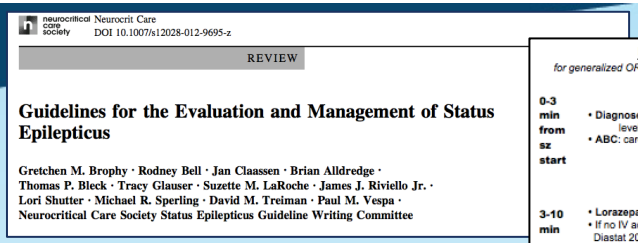
Author Affiliations

Published Online: Mar 31 2020 | https://doi.org/10.1148/radiol.2020201187



TREATMENTS

- Direct CNS infection: supportive, standard neuro-ICU care
  - Seizures -> antiepileptics. If altered>15 minutes after sz, or has no known reason for AMS, cEEG to r/o 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 can't 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


neurocritical care society Neurocrit Care
DOI 10.1007/s12028-012-9695-z

REVIEW

Guidelines for the Evaluation and Management of Status Epilepticus

Gretchen M. Brophy · Rodney Bell · Jan Claassen · Brian Alldredge · Thomas P. Bleck · Tracy Glauser · Suzette M. LaRoche · James J. Riviello Jr. · Lori Shutter · Michael R. Sperling · David M. Treiman · Paul M. Vespa · Neurocritical Care Society Status Epilepticus Guideline Writing Committee

UCSD STATUS EPILEPTICUS GUIDELINE

for generalized OR complex partial status, either continuous or without return to baseline mental status in between seizures

0-3 min from sz start
- **Diagnose:** FSBG, CBC, CMP, coags, AED levels, troponin, ABG, utox, salicylates, EtOH level. Stat noncon head CT or MRI after pt stops seizing.
- **ABC:** cardiac monitor (cycle BP q2min), ensure IV access, intubate if 02 sat low >3min

ONGOING SEIZURE?

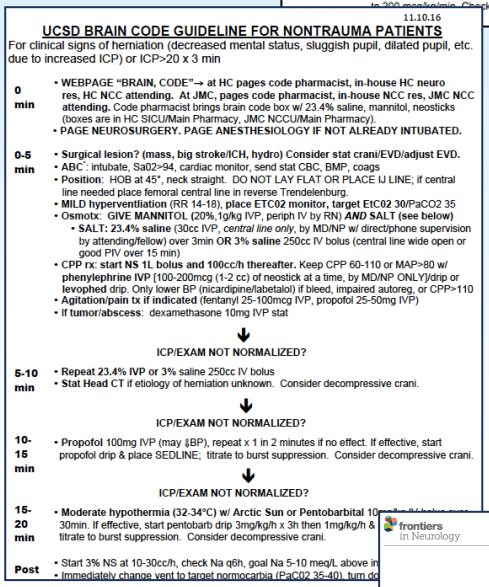
3-10 min
- **Lorazepam 2-4mg IVP STAT. Repeat q5 min until seizures stop (max total 0.1mg/kg)**
- If no IV access, give midazolam 10mg IM/intransal/buccal. If midazolam unavailable, give Diastat 20mg PR (diazepam 20mg IV can be given PR if Diastat unavailable)
- Thiamine 100mg IV and 50mL of D50 IV if low/unknown FSBG
- Page anesthesia to prep for possible intubation

AND
- **Load 1 AED STAT (send pharmacist/RN/tech to pharmacy to obtain immediately):** Fosphenytoin 20mg/kg IV @150mg/min (max 2g, MUST be on cardiac monitor).
  OR
  Valproate 20mg/kg IV over 10 min (do NOT use in surgical or bleeding patients due to risk of platelet dysfxn).
  OR
  If pt is taking Keppra/phenobarbital/topamax at home, or if PHT/VPA are contraindicated, load IV Keppra (50mg/kg IV (up to 4g) at 100mg/min), IV Phenobarbital 20mg/kg IV at 50-100mg/min), or NG/PO Topamax (200-400mg)
  Note: Keppra is NOT FDA approved for treatment of status epilepticus and is less effective than PHT/VPA, so should not be used unless PHT/VPA contraindicated)

ONGOING SEIZURE?

10-20 min
- **Intubation and burst suppressant if generalized status, or vitals unstable. If complex partial status and vitals stable, consider not intubating until minute 20.**
- **After intubation, start burst suppressant, and STAT cEEG / SEDLINE'**
  Midazolam load*: 0.2mg/kg IVP bolus; repeat 0.1-0.2mg/kg boluses q5min until sz stop, up to max total loading dose 2mg/kg. Start IV midazolam drip at 5 mg/h, may increase to max of 50 mg/h. Decrease dose in renal failure. May ↓BP.
  OR
  Propofol load*: 1mg/kg IVP bolus; repeat 1-2mg/kg boluses q3-5min until sz stop, up to max total load 10mg/kg. Start IV propofol drip at 20mcg/kg/min, may increase to 200 mcg/kg/min. Check lactate/trig/y/CK q8h. May ↓BP.

11.10.16


UCSD BRAIN CODE GUIDELINE FOR NONTRAUMA PATIENTS

For clinical signs of herniation (decreased mental status, sluggish pupil, dilated pupil, etc. due to increased ICP) or ICP>20 x 3 min

0 min
- **WEBPAGE "BRAIN, CODE"→ at HC pages code pharmacist, in-house HC neuro res, HC NCC attending. At JMC, pages code pharmacist, in-house NCC res, JMC NCC attending.** Code pharmacist brings brain code box w/ 23.4% saline, mannitol, neosticks (boxes are in HC SICU/Main Pharmacy, JMC NCCU/Main Pharmacy).
- **PAGE NEUROSURGERY. PAGE ANESTHESIOLOGY IF NOT ALREADY INTUBATED.**

0-5 min
- **Surgical lesion? (mass, big stroke/ICH, hydro) Consider stat crani/EVD/adjust EVD.**
- **ABC**: intubate, Sa02>94, cardiac monitor, send stat CBC, BMP, coags
- **Position**: HOB at 45°, neck straight. DO NOT LAY FLAT OR PLACE IJ LINE; if central line needed place femoral central line in reverse Trendelenburg.
- **MILD hyperventliation** (RR 14-18), **place ETC02 monitor, target EtC02 30**/PaCO2 35
- **Osmotx**: **GIVE MANNITOL (20%,1g/kg IVP, periph IV by RN) *AND* SALT (see below)**
  - **SALT: 23.4% saline** (30cc IVP, *central line only*, by MD/NP w/ direct/phone supervision by attending/fellow) over 3min OR **3% saline** 250cc IV bolus (central line wide open or good PIV over 15 min)
- **CPP rx: start NS 1L bolus and 100cc/h thereafter.** Keep CPP 60-110 or MAP>80 w/ **phenylephrine IVP** [100-200mcg (1-2 cc) of neostick at a time, by MD/NP ONLY]/drip or **levophed** drip. Only lower BP (nicardipine/labetalol) if bleed, impaired autoreg, or CPP>110
- **Agitation/pain tx if indicated** (fentanyl 25-100mcg IVP, propofol 25-50mg IVP)
- **If tumor/abscess**: dexamethasone 10mg IVP stat

ICP/EXAM NOT NORMALIZED?

5-10 min
- **Repeat 23.4% IVP or 3%** saline 250cc IV bolus
- **Stat Head CT** if etiology of herniation unknown. Consider decompressive crani.

ICP/EXAM NOT NORMALIZED?

10-15 min
- **Propofol** 100mg IVP (may ↓BP), repeat x 1 in 2 minutes if no effect. If effective, start propofol drip & place SEDLINE; titrate to burst suppression. Consider decompressive crani.

ICP/EXAM NOT NORMALIZED?

15-20 min
- **Moderate hypothermia (32-34°C) w/ Arctic Sun or Pentobarbital 10**
  30min. If effective, start pentobarb drip 3mg/kg/h x 3h then 1mg/kg/h & titrate to burst suppression. Consider decompressive crani.

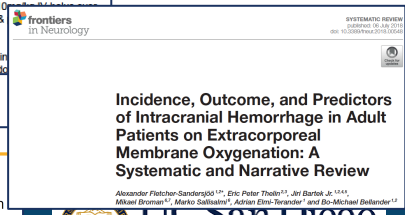
Post
- Start 3% NS at 10-30cc/h, check Na q6h, goal Na 5-10 meq/L above in
- Immediately change vent to target normocarbia (PaC02 35-40), turn do


PLOS ONE

RESEARCH ARTICLE

Management of intracranial hemorrhage in adult patients on extracorporeal membrane oxygenation (ECMO): An observational cohort study

Alexander Fletcher-Sandersjöö[1,2]*, Eric Peter Thelin[2,3], Jiri Bartek, Jr.[1,2,4,5], Adrian Elmi-Terander[1], Mikael Broman[6,7], Bo-Michael Bellander[1,2]


frontiers in Neurology

SYSTEMATIC REVIEW

Incidence, Outcome, and Predictors of Intracranial Hemorrhage in Adult Patients on Extracorporeal Membrane Oxygenation: A Systematic and Narrative Review

Alexander Fletcher-Sandersjöö[1,2]*, Eric Peter Thelin[2,3], Jiri Bartek Jr.[1,2,4,5], Mikael Broman[6,7], Marko Sallisalmi[8], Adrian Elmi-Terander[1] and Bo-Michael Bellander[1,2]

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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

Mazen Odish
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