COVID-19

KEY FACTS

TERMINOLOGY

- COVID-19 = disease caused by SARS-CoV-2 virus
  - Same clade (ancestor) as SARS-CoV, MERS-CoV

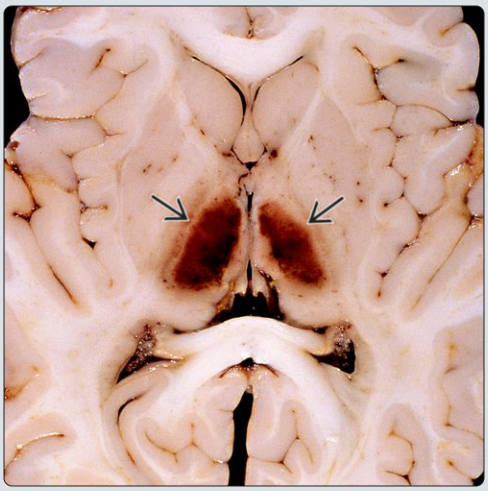
IMAGING

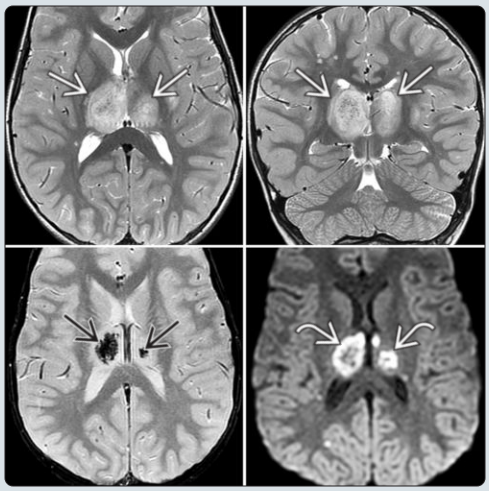
- > 50% of MRs in ICU patients with neurologic symptoms are normal!
- Findings vary widely with etiology
  - Patchy bilateral ground-glass opacities in lungs
    - Look for on CTA of cervicothoracic vessels
    - Look for thrombi in pulmonary veins
  - Strokes
    - Large cerebral vessel occlusion ± infarct
      - Both arterial, venous
    - Multiple embolic infarcts (DWI best)
  - Hypoxic-ischemic encephalopathy
    - Hypodense basal ganglia
    - Cortical restriction on DWI
      - Also occurs with nonconvulsive status epilepticus ± ipsilateral thalamus
  - Acute necrotizing encephalopathy (ANE)
    - Bilateral hypodensities medial thalami
    - Restricted diffusion on DWI
    - ± hemorrhage on T2* GRE or SWI
  - Acute hemorrhagic leukoencephalopathy (AHLE)
    - Do MR with DWI, SWI
      - Look for "blooming black dots" (microbleeds)
    - Contrast may be contraindicated if multiorgan failure
  - Meningoencephalitis
    - Pial ("leptomeningeal") enhancement
  - Viral or autoimmune encephalitis
    - Cortical hyperintensity on FLAIR

PATHOLOGY

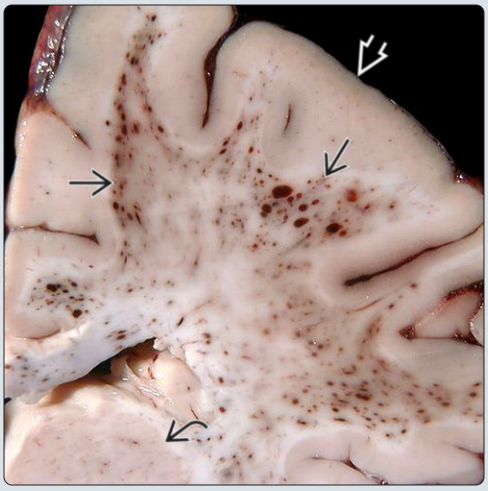
- SARS-CoV-2 requires ACE2 as cell entry receptor
  - ACE2 receptor widely expressed in neurons → neuroinvasive

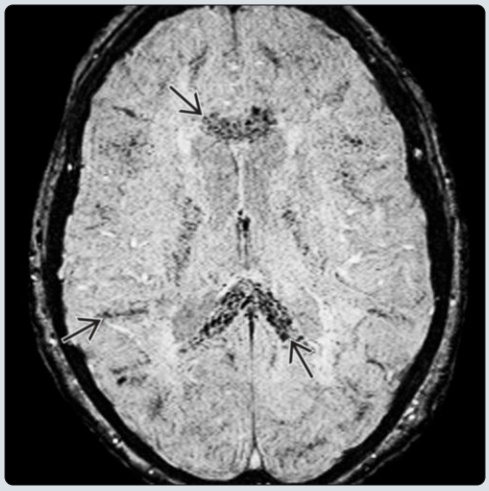
(Left) *Autopsied case of acute necrotizing encephalopathy (ANE) shows bilateral hemorrhagic necrosis in the medial thalami. (Courtesy R. Hewlett, MD).* **(Right)** *Virus-associated ANE in an obtunded 5-year-old girl shows bilateral medial thalamic hyperintensities on T2WI. T2* GRE shows hemorrhagic foci. DWI shows restricted diffusion in the lesions. In this case, the etiology was influenza A, but the pathology is identical to ANE caused by SARS-CoV-2.*





(Left) *Coronal autopsied case of acute hemorrhagic leukoencephalopathy (AHLE) shows innumerable petechial hemorrhages in the subcortical and deep white matter (WM) extending into the subcortical U-fibers. Note striking sparing of the cortex and basal ganglia. Findings are identical in critical illness-associated cerebral microbleeds.* **(Right)** *Axial T2* SWI in a case of viral infection and acute clinical deterioration show multiple tiny WM microbleeds. AHLE was confirmed by biopsy.*





TERMINOLOGY

Abbreviations

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
- Coronavirus disease 2019 (COVID-19)
- Angiotensin converting enzyme 2 receptor (ACE2)

Definitions

- COVID-19 = disease caused by SARS-CoV-2 virus
  - Is zoonosis (disease transmitted to humans from animals)

IMAGING

General Features

- Best diagnostic clue
  - Patchy bilateral ground-glass opacities in lungs
    - Look for findings on cervicothoracic CTA
- Coronavirus is neurotropic but CNS findings vary widely
  - Evidence of vascular endothelial damage, hypercoagulability
    - Kawasaki disease
    - Multiorgan intravascular thrombosis
      - Large vessel occlusion ± infarct
      - Thrombus in cervical internal carotid artery (ICA) or middle cerebral artery (MCA)
  - Evidence of hypoxic-ischemic encephalopathy (HIE)
    - Early: Symmetric hypodense basal ganglia
    - Late: Diffuse cerebral edema
  - Acute necrotizing encephalopathy (ANE)
    - Bilateral hypodensities medial thalami
    - ± hemorrhagic foci
  - Acute hemorrhagic leukoencephalopathy (AHLE)
    - May be normal unless focal macrobleed(s)
  - Meningoencephalitis
    - Pial ("leptomeningeal") enhancement
  - Viral or autoimmune encephalitis
    - Cortical hyperintensity on FLAIR

CT Findings

- Varies widely; often normal

MR Findings

- T1WI
  - > 50% of MRs in ICU patients with neurologic symptoms are normal!
  - ± hypointense basal ganglia, thalami
- T2WI
  - ± changes of HIE with hyperintense globi pallidi
- FLAIR
  - Most common = cortical hyperintensity (37%)
  - Subcortical/deep white matter hyperintensities
  - ± changes of HIE with hyperintense globi pallidi
    - Hyperintense hippocampi
- T2* GRE
  - Shows macrobleeds (e.g., cortical blooming)
  - Microbleeds may not be visible; corpus callosum splenium may be subtly hypointense
- DWI
  - Cortical restricted diffusion common
  - HIE: Symmetric restricted diffusion, usually basal ganglia
    - Globus pallidi commonly affected
  - If nonconvulsive status epilepticus, may show hippocampus with ipsilateral thalamus restriction
- T1WI C+
  - Leptomeningeal enhancement
- SWI
  - Look for "blooming black dots" (microbleeds)
  - Occurs with AHLE, critical illness-associated microbleeds
  - Subcortical, deep white matter (especially corpus callosum)
  - Generally spares cortex ± basal ganglia

Imaging Recommendations

- Protocol advice
  - MR with DWI, SWI
  - Contrast may be contraindicated if multiorgan failure

DIFFERENTIAL DIAGNOSIS

Acute Cerebral Ischemia-Infarction

- Look for hypercoagulable state
- Look for intravascular clots in other organs

Acute Hemorrhagic Leukoencephalitis

- Hyperacute, fulminant part of acute disseminated encephalomyelitis (ADEM) spectrum
- Microbleeds in white matter; cortex typically spared
  - FLAIR, GRE can be normal; use SWI

Acute Necrotizing Encephalitis

- Bithalamic infarcts can also occur with internal cerebral vein thrombosis

Critical Illness-Associated Cerebral Microbleeds

- Common in patients with respiratory failure
- Pneumonia, septic shock common
- Often on ventilator assistance or ECMO
- Similar in etiology, appearance to high-altitude cerebral edema (HACE)
- Typically spare deep gray matter, cortex

Hypoxic-Ischemic Encephalopathy

- Common complication in COVID-19

PATHOLOGY

Gross Pathologic & Surgical Features

- Major CNS pathologies
  - Dysregulated host immune response → "cytokine storm syndrome" → direct CNS damage
    - ANE
      - Life-threatening complication of viral infection
      - Most often seen with influenza but reported in COVID-19
      - Usually children, young adults
    - Demyelination/autoimmune encephalitis
      - Systemic inflammatory response syndrome (SIRS)
  - Coagulopathy with ↑ D-dimer, vascular endothelial dysfunction
    - Prolonged activated partial-thromboplastin time (aPTT)
      - 90% positive for lupus anticoagulant

- Associated factor XII deficiency common
- Venous thrombosis common
- Thromboembolic strokes
- Large vessel occlusions (both arterial, venous) 5%
- Multiple small emboli
- Disseminated intravascular coagulation (DIC)
- AHLE (Weston-Hurst disease)
- Focal hemorrhages &/or innumerable microbleeds
- Critical illness-associated cerebral microbleeds
- Seen in patients with acute respiratory distress syndrome (ARDS), often on ventilator/ECMO
- Similar physiology to HACE

Etiology

- Coronaviruses are single-stranded RNA viruses
- Found in animals (bats, pigs, mice, cattle, humans)
- Prior known human CoVs (HKU1, NL63, OC43, hCoV-229E) caused mild respiratory diseases
- Coronavirus epidemics with previously unknown CoVs
  - 2003: SARS-CoV (mortality 9-10%)
  - 2008: MERS-CoV (mortality 37%)
  - 2019: SARS-CoV-2
    - Same clade (ancestor) as SARS-CoV, MERS-CoV
    - Mortality still TBD; estimated 1-2% (10x seasonal influenza)
- Possible entry routes of SARS-CoV-2 into CNS
  - Neuronal retrograde route of CNS entry
    - Through cribriform plate (retrograde along olfactory tract)
    - Receptor neurons of trigeminal nerve in nasal cavity or sensory fibers of vagus nerve in brainstem
  - Hematogeneous dissemination of infected leukocytes through compromised blood-brain barrier (BBB)
    - Transcytosis across brain microvascular endothelial cells and pericytes by endocytic vesicles
    - Directly infect endothelial/epithelial cells to pass across BBB or blood-CSF barrier in choroid plexus
- SARS-CoV-2 requires ACE2 as cell entry receptor
  - Crown or wreath-like spike glycoproteins bind SARS-CoV-2 to cell membranes
    - With high affinity for ACE2 (10-20x SARS-CoV)
  - Neuroinvasive (ACE2 receptor widely expressed in neurons, endothelial cells > glia)
    - Brainstem nuclei especially affected
      - Nucleus solitarius, nucleus ambiguus
      - May contribute to severe respiratory dysfunction

CLINICAL ISSUES

Presentation

- Most common signs/symptoms
  - Fever (80-99%) but only in 40-50% at initial presentation
  - "Dry" cough (50-85%)
  - Respiratory distress, dyspnea (55%)
    - 5-8 days after 1st symptoms
    - 15% develop ARDS, often within 24-48 hours
  - Myalgia (30-50%)
  - Neurologic
    - Initial presentation
      - Anosmia (highly suggestive), loss of taste
      - Headache (nonspecific)
      - Acute stroke (6%)
    - Hospitalized in ICU (≈ 20-85% develop neurologic signs)
      - Altered mental status
      - Seizures
- Other signs/symptoms
  - Sore throat 15% (rhinorrhea/nasal congestion rare vs. common cold)
  - Gastrointestinal 14%: Loss of appetite, nausea and vomiting, diarrhea (but 3% sole initial symptom)

Demographics

- Any age but most vulnerable = ≥ 60 years
- Transmissibility
  - Droplets (estimated 3-6')
  - Fomites (high; surfaces)
- Infectivity
  - R_0 = 2.2-2.5 (vs. measles = 15-18, seasonal influenza = 1)
  - Household attack rate 10-15% vs. other close contacts 1-2%

Natural History & Prognosis

- Varies widely from asymptomatic to death
  - Hypoxia
  - Multiorgan failure
- 25-50% develop ≥ 1 comorbidity
- 25-80% of hospitalized patients develop neurologic manifestations during disease course
  - Impaired consciousness, altered mental status
  - Strokes
  - Febrile seizures (both convulsive, nonconvulsive status epilepticus)

Treatment

- Antivirals (e.g., remdesivir)

DIAGNOSTIC CHECKLIST

Consider

- Add T1 C+ FS, SWI to MR protocol (evaluate for meningoencephalitis, microbleeds)

Reporting Tips

- COVID-19 patients typically present with fever, cough, and dyspnea
- Small number of patients may present with unrelated complaints (such as trauma/stroke)
- Evaluate lung parenchyma on CT spine imaging and CT angiography for nonpulmonary reasons
  - Unsuspected/incidental lung findings, may lead to further investigations and diagnosis of COVID-19

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TOO MUCH TEXT

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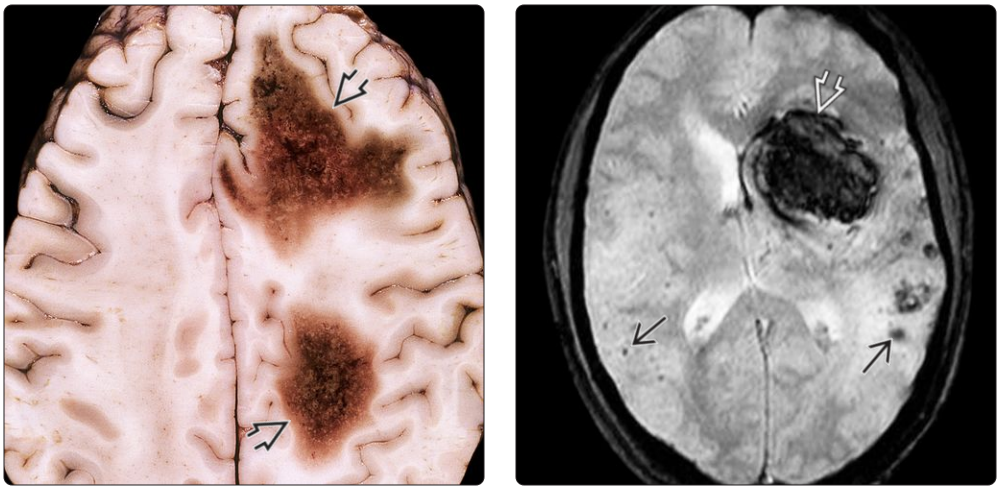
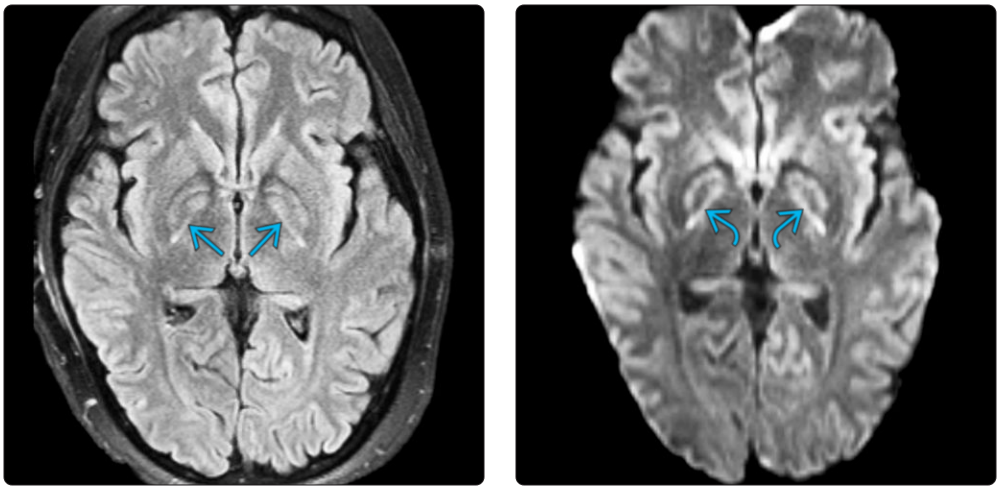
(Left) *Gross autopsy shows 2 areas of gross hemorrhagic necrosis in the left hemispheric WM. Findings and clinical history of prior flu-like illness with a rapidly progressive clinical course are characteristic of a viral exanthem with AHLE. (Courtesy R. Hewlett, MD.)* **(Right)** *Axial T2* GRE in a patient with rapid decline after a flu-like viral illness shows a large left frontal hemorrhage with numerous blooming foci in multiple subcortical WM lesions. This is AHLE. (Courtesy R. Ramakantan, MD).*



(Left) *Axial FLAIR MR in a 32-year-old man with COVID-19 on intubation who developed altered mental status shows symmetric hyperintensity in the globi pallidi.* **(Right)** *Axial DWI in the same patient shows mild restricted diffusion in the outer margins of both globi pallidi. Hypoxic-ischemic encephalopathy (HIE) is common in patients with severe COVID-19, and the globus pallidi are commonly affected.*



(Left) *Axial NECT scan in a 42-year-old man with COVID-19 was obtained shortly before the patient expired. Severe cerebral edema is present, seen here as diffuse low-density brain with effacement of all basilar cisterns. Both hemispheres and the cerebellum are affected.* **(Right)** *More cephalad NECT shows the gray matter-WM interfaces are completely effaced. The lateral ventricles are small, and the surface sulci are obliterated. The patient was pronounced brain dead shortly after the scan was obtained.*