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Neurologic complications of COVID-19

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COVID-19

- 1300s: Plague killed 25 million in Europe
- 1600s: Small pox killed 20 million in North America
- 19181919: Influenza killed 3050 million
- 1980s – now: AIDS killed 36 million worldwide

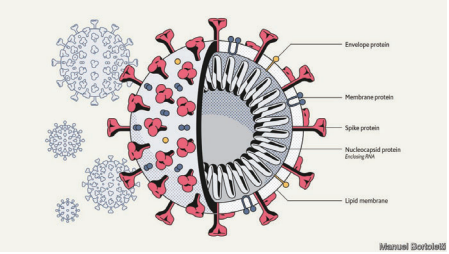
Source: https://coronavirus.jhu.edu/map.html

OVERVIEW

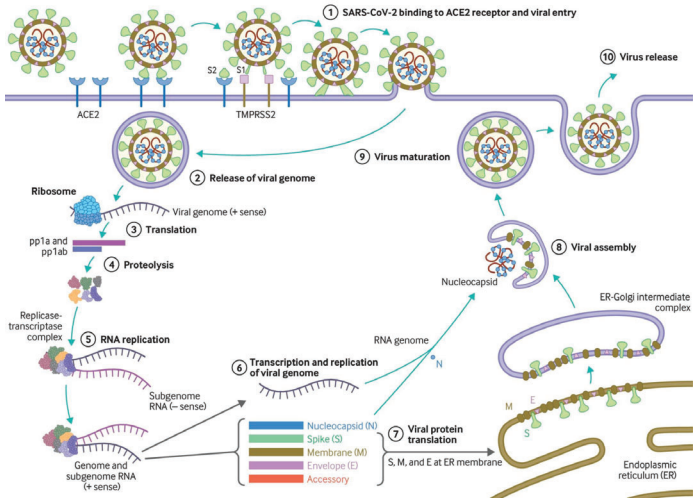
1. SARS-CoV-2
2. NEUROLOGIC SYMPTOMS IN ACUTE COVID-19
3. NEUROLOGIC COMPLICATIONS OF SEVERE COVID-19
4. PARA AND POST-INFECTIOUS COMPLICATIONS
5. POST-ACUTE COVID SYNDROME

COVID-19

- SARS-CoV-2 is a coronavirus
- Other coronaviruses include SARS-CoV-1 (2003) and MERS-CoV (2012)
- Acute respiratory illness



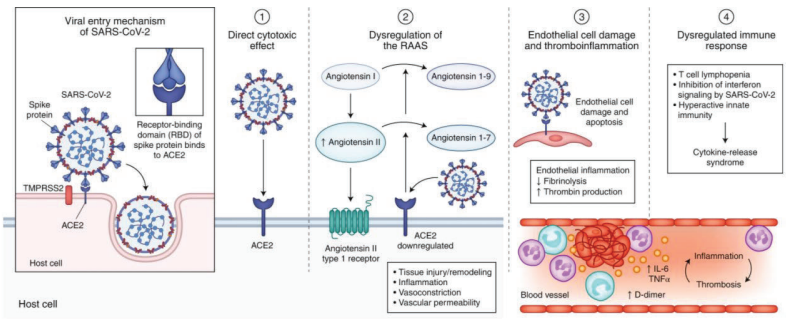
SARS-CoV-2 ENTRY AND REPLICATION



Cevik M, Virology, transmission, and pathogenesis of SARS-CoV-2, BMJ 2020

COVID-19 AND IMMUNOPATHOGENESIS

From: Extrapulmonary manifestations of COVID-19



Gupta A et al. Extrapulmonary manifestations of COVID19. Nature Medicine July 2020

NEUROLOGIC COMPLICATIONS OF COVID-19

	SYMPTOMS OR SYNDROMES	RELATION TO DISEASE COURSE	FREQUENCY
Neurologic symptoms of COVID-19	Anosmia, dysgeusia, headache, dizziness, paresthesias	Early	Common
Neurologic complications of severe COVID-19	Encephalopathy, Stroke, ANE, seizures	Late	Common in severe disease
Direct involvement of CNS with SARS CoV-2	Meningoencephalitis	Unknown	Extremely rare
Para-infectious and Post-infectious complications of SARS CoV-2	GBS, Miller Fisher syndrome, ADEM	7 to 10 days after onset	Rare
Neurologic complications after acute COVID-19	Brain fog, Dysautonomia, Headaches	12 weeks after onset	Common

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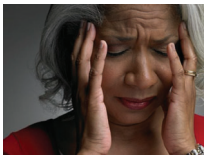
NEUROLOGIC SYMPTOMS IN ACUTE COVID-19

COVID-19 AND NEUROLOGY COMPLAINTS

94% of patients have some neurologic complain

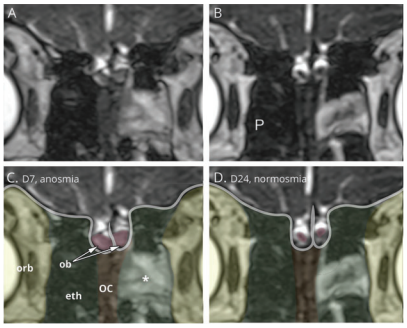
- Headaches: 45% to 80%
- Loss of smell: 65% to 85%
- Loss of taste: 55% to 88%
- Muscle pain: 57% to 63%
- Dizziness: 8 to 16%
- Nerve pain



Source: Yousaf A et. al Clin Infect Dis, July 2020, Somani S et al. Neurohospitalist 2020

ANOSMIA AND AGEUSIA

- Loss of taste secondary to loss of smell
- Can lead to weight loss
- ACE2 receptors in nasal mucosa
- Transient olfactory bulb edema



Source: Laurendon et. al Bilateral transient olfactory bulb edema during COVID19-related anosmia. May 2020

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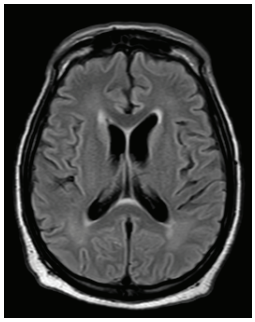
NEUROLOGIC COMPLICATIONS OF SEVERE COVID-19

CASE

- 59 yo M with DM, HTN,tx to UAB for worsening hypoxemia from COVID-19 PNA
- Intubated immediately upon arrival
- Paralyzed,Proned, Remdesivir
- Septic shock, AKI, Tracheostomy, PEG
- 30 days into hospitalization – not following commands, not waking up
- LTEEG: Diffuse slowing, disorganization



NEUROLOGIC COMPLICATIONS IN HOSPITALIZED PATIENTS

ANNALS of Clinical and Translational Neurology — Open Access — ANA AMERICAN NEUROLOGICAL ASSOCIATION

RESEARCH ARTICLE

Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients

Eric M. Liotta[a], Ayush Batra[a], Jeffrey R. Clark, Nathan A. Shlobin, Steven C. Hoffman, Zachary S. Orban & Igor J. Koralnik

Ken & Ruth Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

- Hospitalized patients
- Retrospective analysis

NEUROLOGIC COMPLICATIONS IN HOSPITALIZED PATIENTS

- 509 patients
- Neurologic manifestations:
  - At onset in 215 patients (42.2%)
  - At hospital admission in 319 patients (62.7%)
  - at any time during the disease course in 419 patients (82.3%)
- Common symptoms included myalgias, headaches, encephalopathy, dizziness, dysgeusia, and anosmia, generalized fatigue.

Liotta et al. Frequent neurologic manifestations and encephalopathyassociated morbidity in Covid-19 patients. Annals of Clinical and Translational Neuorlogy, Sept 2020

NEUROLOGIC COMPLICATIONS IN HOSPITALIZED PATIENTS

Table 1. Patient characteristics by presence of neurologic manifestations and encephalopathy.

	Overall	No Neurologic Manifestation	Any Neurologic Manifestation	*P*	No Encephalopathy	Encephalopathy	*P*
n	509	90	419		347	162	
Age, years (mean (SD))	58.51 (16.93)	62.98 (18.97)	57.53 (16.31)	0.005	55.22 (16.10)	65.51 (16.54)	<0.001
Male, *n* (%)	281 (55.2)	50 (55.6)	231 (55.1)	1	180 (51.9)	101 (62.3)	0.034
Female, *n* (%)	228 (44.8)	40 (44.4)	188 (44.9)		167 (48.1)	61 (37.7)	
Race, *n* (%)				0.227			0.204
White	268 (52.7)	56 (62.2)	212 (50.6)		172 (49.6)	96 (59.3)	
Black or African American	151 (29.7)	26 (28.9)	125 (29.8)		114 (32.9)	37 (22.8)	
Asian	18 (3.5)	2 (2.2)	16 (3.8)		12 (3.5)	6 (3.7)	
Native Hawaiian or Other Pacific Islander	1 (0.2)	0 (0.0)	1 (0.2)		0 (0.0)	1 (0.6)	
Other	53 (10.4)	3 (3.3)	50 (11.9)		37 (10.7)	16 (9.9)	
Unknown	1 (0.2)	0 (0.0)	1 (0.2)		1 (0.3)	0 (0.0)	
Declined to provide	17 (3.3)	3 (3.3)	14 (3.3)		11 (3.2)	6 (3.7)	
Ethnicity, *n* (%)				0.075			0.23
Not Hispanic or Latino	384 (75.4)	75 (83.3)	309 (73.7)		263 (75.8)	121 (74.7)	
Hispanic or Latino	107 (21.0)	11 (12.2)	96 (22.9)		75 (21.6)	32 (19.8)	
Declined to Provide	18 (3.5)	4 (4.4)	14 (3.3)		9 (2.6)	9 (5.6)	
Time from COVID Onset to Hospitalization, days (median [IQR])	7.00 [4.00, 9.59]	5.00 [2.00, 8.98]	7.00 [4.00, 10.00]	0.003	7.00 [4.00, 10.00]	6.00 [3.00, 9.00]	0.014
Hospitalized at the Academic Medical Center, *n* (%)	254 (49.9)	32 (35.6)	222 (53.0)	0.004	168 (48.4)	86 (53.1)	0.375

Liotta et al. Frequent neurologic manifestations and encephalopathyassociated morbidity in Covid-19 patients. Annals of Clinical and Translational Neuorlogy, Sept 2020

NEUROLOGIC COMPLICATIONS IN HOSPITALIZED PATIENTS

	Overall	No Neurologic Manifestation	Any Neurologic Manifestation	*P*	No Encephalopathy	Encephalopathy	*P*
n	509	90	419		347	162	
Medical Comorbidities							
History of Any Neurological Disorder, *n* (%)	134 (26.3)	27 (30.0)	107 (25.5)	0.459	79 (22.8)	55 (34.0)	0.010
Cancer, *n* (%)	61 (12.0)	10 (11.1)	51 (12.2)	0.919	29 (8.4)	32 (19.8)	<0.001
Cerebrovascular Disease, *n*(%)	39 (7.7)	12 (13.3)	27 (6.4)	0.044	18 (5.2)	21 (13.0)	0.004
Chronic Kidney Disease, *n* (%)	56 (11.0)	10 (11.1)	46 (11.0)	1	29 (8.4)	27 (16.7)	0.008
Diabetes Mellitus, *n* (%)	154 (30.3)	31 (34.4)	123 (29.4)	0.408	95 (27.4)	59 (36.4)	0.049
Dyslipidemia, *n* (%)	172 (33.8)	32 (35.6)	140 (33.4)	0.789	100 (28.8)	72 (44.4)	0.001
Heart Failure, *n* (%)	36 (7.1)	7 (7.8)	29 (6.9)	0.951	14 (4.0)	22 (13.6)	<0.001
Hypertension, *n* (%)	277 (54.4)	55 (61.1)	222 (53.0)	0.198	169 (48.7)	108 (66.7)	<0.001
Organ transplantation, *n* (%)	16 (3.1)	2 (2.2)	14 (3.3)	0.827	7 (2.0)	9 (5.6)	0.063
Peripheral Vasc. Disease, *n* (%)	10 (2.0)	4 (4.4)	6 (1.4)	0.147	4 (1.2)	6 (3.7)	0.112
Smoking, *n* (%)	140 (27.5)	22 (24.4)	118 (28.2)	0.558	83 (23.9)	57 (35.2)	0.011
Patient outcomes							
Hospital length of stay, days (median [IQR])	7.00 [3.24, 13.00]	5.00 [2.00, 8.00]	8.00 [4.00, 14.00]	<0.001	6.00 [3.00, 8.00]	17.00 [11.00, 25.00]	<0.001
Modified Rankin Scale Score at Hospital Discharge, *n*(%)				0.093			<0.001
0 to 2: Looks after own affairs without assistance	362 (71.1)	63 (70.0)	299 (71.4)		310 (89.3)	52 (32.1)	
3: Ambulates unassisted, needs some help with own affairs	47 (9.2)	5 (5.6)	42 (10.0)		18 (5.2)	29 (17.9)	
4 to 5: Unable to ambulate unassisted, needs assistance with own bodily care	57 (11.2)	9 (10.0)	48 (11.5)		8 (2.3)	49 (30.2)	
6: dead	43 (8.4)	13 (14.4)	30 (7.2)		11 (3.2)	32 (19.8)	
30-day mortality, *n* (%)	46 (9.1)	13 (14.4)	33 (7.9)	0.079	11 (3.2)	35 (21.7)	<0.001

Liotta et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Annals of Clinical and Translational Neuorlogy, Sept 2020

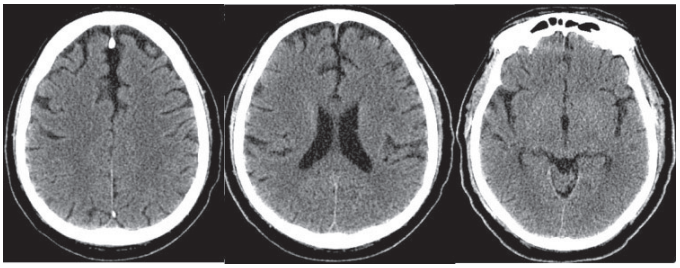
ENCEPHALOPATHY- CAUSES

- Hypoxia
- Metabolic derangements
- Seizures
- Delirium
  - Sedatives
  - Anti-cholinergics
  - Steroids

Nath A. Neurologic Manifestations of Severe Acute Respiratory Syndrome Coronavirus 2. Continuum, Aug 2021

CASE

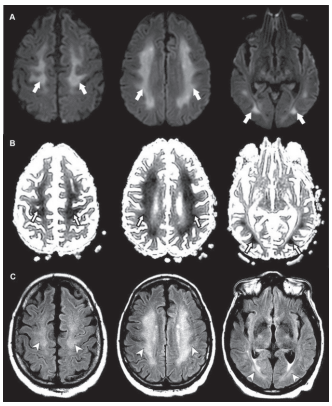
- 59 yo M with DM, HTN, known COVID exposure presented with hypoxemia. O2 sat: 61%
- Intubated, RT-PCR positive for SARS-CoV-2
- Patient unable to arouse 2 weeks after admission



Vines BL, Agnihotri SP. Delayed post-hypoxic leukoencephalopathy in an adult with COVID-19. *J Neurovirol*. 2021;27(3):514-518

CASE

- Remains difficult to arouse, unable to follow commands or move limbs
- MRI at 1 month



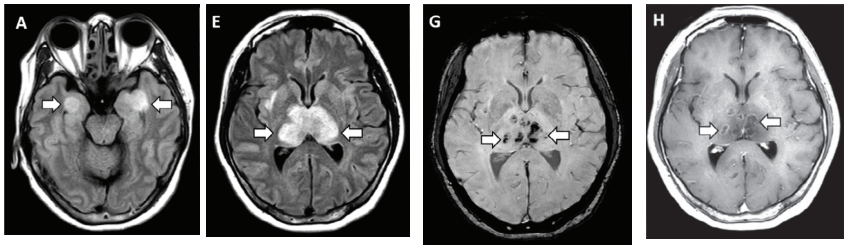
Vines BL, Agnihotri SP. Delayed post-hypoxic leukoencephalopathy in an adult with COVID-19. *J Neurovirol*. 2021;27(3):514-518

COVID ASSOCIATED LEUKOENCEPHALOPATHY

- Delayed post-hypoxic leukoencephalopathy
- Microhemmorhagic leukoencephalopathy
- ADEM
- PRES

ACUTE NECROTIZING ENCEPHALOPATHY RELATED TO COVID-19

- Case report
- Airline worker, F, late 50s – fever, cough, AMS
- CSF analysis limited due to traumatic tap, SARS-CoV-2 PCR in CSF not done
- CTA, CTV normal

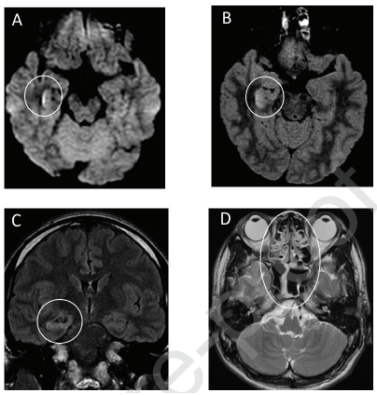


Poyiadji N, Shahin G, et al. COVID19-associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features. Radiology. 2020;201187.

VIRAL ENCEPHALITS

- 24 yo M, Japan, with HA, fatigue, fever
- Day 5: Worsening HA, sore throat
- Day 9: AMS, seizures
- CSF: OP of 32cmH2O, 12 WBCs
- SARS CoV-2 detected in CSF, but no in nasopharyngeal swab

- Extremely rare
- SARS-CoV-2 not detected in most CSF samples



Moriguchi et al. A first Case of Meningitis/Encephalitis associated with SARS-Coronavirus-2. Int Journal Inf Diseases 2020

NEUROPATHOLOGY OF COVID-19

Table 1. Gross Findings and Results of Histologic Analysis to Detect SARS-CoV-2.*

Patient No.	Days from Symptom Onset to Death	Hours from Death to Autopsy	Gross Inspection		Histologic Analysis
			Brain Volume	Observations	
			grams		
1	20	52	1290	No gross abnormalities	Acute hypoxic ischemic damage, mild arteriolosclerosis
2	6	32	1460	Moderate atherosclerosis	Acute hypoxic ischemic damage
3	12	21	1210	Moderate atherosclerosis, chronic infarcts	Acute hypoxic ischemic damage, chronic infarcts, mild arteriolosclerosis
4	6	36	1150	Moderate-to-severe atherosclerosis, pale substantia nigra and locus coeruleus	Acute hypoxic ischemic damage, moderate arteriolosclerosis, pathological features of Lewy body disease and Alzheimer's disease
5	9	40	1460	No gross abnormalities	Acute hypoxic ischemic damage
6	0	77	1330	Mild atherosclerosis	Acute hypoxic ischemic damage, moderate arteriolosclerosis, focal leptomeningeal chronic inflammation
7	2	54	1300	Moderate atherosclerosis, cortical atrophy	Acute hypoxic ischemic damage, mild arteriolosclerosis, pathological features of Alzheimer's disease
8	2	32	1350	Moderate atherosclerosis, chronic infarcts	Acute hypoxic ischemic damage, chronic infarcts, moderate arteriolosclerosis
9	23	23	1330	Mild atherosclerosis	Acute hypoxic ischemic damage, mild arteriolosclerosis
10	7	21	1120	Moderate atherosclerosis, anaplastic astrocytoma tumor resection cavity	Acute hypoxic ischemic damage, recurrent or residual anaplastic astrocytoma
11	26	41	1090	No gross abnormalities	Acute hypoxic ischemic damage, Alzheimer's type II astrocytosis
12	6	45	1130	Mild atherosclerosis, pale substantia nigra	Acute hypoxic ischemic damage, mild arteriolosclerosis, pathological features of Lewy body disease and Alzheimer's disease
13	12	61	1300	No gross abnormalities	Acute hypoxic ischemic damage, mild arteriolosclerosis, focal perivascular chronic inflammation, Alzheimer's type II astrocytosis

Solomon I et al. Neuropathological features of Covid-19 NEJM June 12, 2020

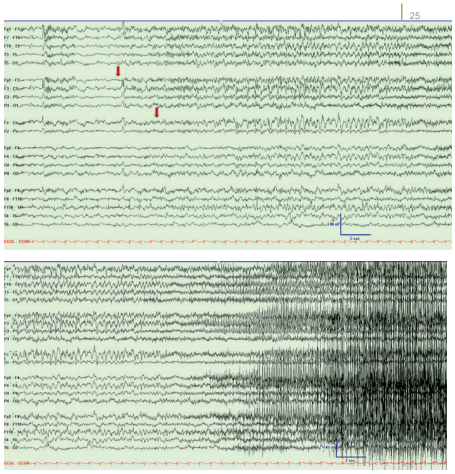
ONDINE'S CURSE

- Central hypoventilation syndrome
- Often discussed in context of COVID-19
- No concrete evidence
- Brainstem pathology
- ?Direct involvement of brainstem by the virus

Nath A. Neurologic Manifestations of Severe Acute Respiratory Syndrome Coronavirus 2. Continuum, Aug 2021

CASE

- 49 yo F with schizoaffective disorder, conversion disorde presented with AMS
- CT head normal
- No known exposure, initial RT-PCR was negative
- Continuous video EEG monitoring showed multiple seizures
- Developed fever within 24 hours and repeat test was positive
- MRI Brain no focal deficits



Somani S et al. De Novo Status Epilepticus in patients with COVID-19. Ann Clin Transl Neurol. 2020 Jul; 7(7): 1240–1244.

SEIZURES IN COVID-19

- New onset status epilepticus
- Breakthrough seizures in patients with epilepsy
- Multi-institutional study of hospitalized patients with COVID-19
- N= 197
- Electrographic seizures: 19 (9.6%) patients
  - Nonconvulsive status epilepticus (NCSE) in 11 (5.6%)
- Risk factors: Pre-existing clinical seizures, intracranial lesions
- Independent predictor of in-hospital mortality

Lin L et al. Electroencephalographic Abnormalities are Common in COVID-19 and are Associated with Outcomes Ann Neurol, 89: 872-883

STROKES IN COVID-19

- Both arterial and venous hypercoagulable state
- Single center study of 219 patients with COVID-19
- 4.6% had Acute ischemic stroke
- 0.5% had ICH

Presentation
- Cerebral venous thrombosis
- Ischemic stroke with multiple arterial occlusions
- Microhemorrhages

Pathophysiology
- Coagulopathy
- Antiphospholipid antibodies
- Cardiac embolism
- Endothelitis

Risk factors
- Myocarditis
- Known vascular risk factors
- Acute respiratory distress syndrome
- Multiorgan impairment

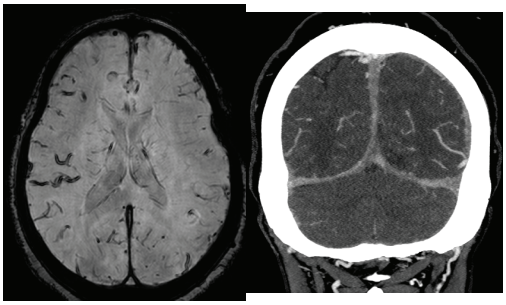
CONTINUUM: LIFELONG LEARNING IN NEUROLOGY

Li Y, Li M, Wang M, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke Vasc Neurol 2020;5(3):279–284
Nath A. Neurologic Manifestations of Severe Acute Respiratory Syndrome Coronavirus 2. Continuum, Aug 2021

CASE

- 67 yo F with neurosarcoidosis (pachymeningitis), on MTX, presented with blurry vision, headache. Did not improve with steroids
- 1 month prior had mild COVID-19, did not require hospitalization

Venous sinus thrombosis



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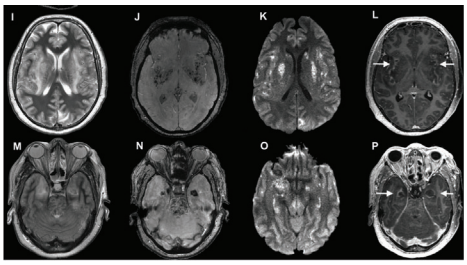
PARA AND POST INFECTIOUS NEUROLOGIC COMPLICATIONS

PARA AND POSTINFECTIOUS COMPLICATIONS

- Can occur soon after initial symptoms of COVID-19 or few weeks later
- Immune mediated mechanisms
- ?Molecular mimicry

ADEM

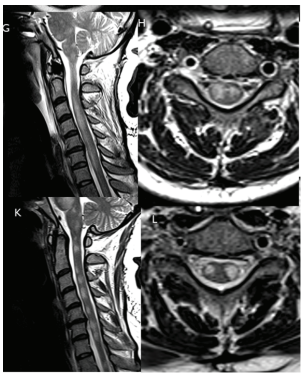
- Acute Disseminated Encephalomyelitis
- Typically seen in children but described in many adults with COVID-19
- Seen with both mild and severe COVID-19
- Encephalopathy with other neurologic symptoms
- Hemorrhagic changes are frequently seen on MRI
- Responds to corticosteroids



Ross P et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain October 2020, Volume 143 (10)

TRANSVERSE MYELITIS

- Transverse or Longitudinal
- Seen with both mild and severe COVID-19
- Involvement of ventral gray
- Can be part of ADEM
- Extensive acute necrotizing myelitis is also described
- SARS-CoV-2 not detected in CSF
- Lympocytic pleocytosis
- Other ab not detected
- Responds to corticosteroids and PLEX



Ross P et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain October 2020, Volume 143 (10)

GBS

- Guillain-Barre syndrome
- Systemic review performed
- Seen in children and adults: 11 to 94 years
- 68.5% were in males
- Most patients had moderate to severe COVID-19
- CSF SARS CoV-2 absent in CSF
- Miller Fischer variant reported

Nath A. Neurologic Manifestations of Severe Acute Respiratory Syndrome Coronavirus 2. Continuum, Aug 2021
Abu-Rumeileh S, Abdelhak A, Foschi M, et al. Guillain-Barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases. J Neurol 2021;268(4):1133-1170.

GBS ASSOCIATED WITH COVID-19

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 mm^3; 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 mm^3; 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.

Toscano et al. **Guillain–Barré Syndrome Associated with SARS-CoV-2 NEJM** April 17, 2020

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POST-COVID SYNDROME AND NEUROLOGIC SEQUELAE

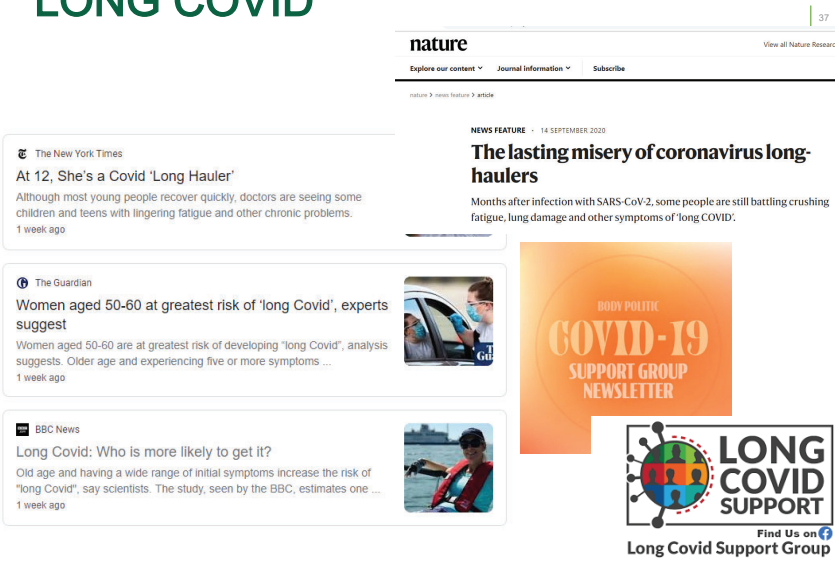
"LONG COVID"

- Illness in people who have either:
- Recovered from COVID-19 but still report lasting effects of the infection

OR

- Have had the usual symptoms for far longer than would be expected

“LONG COVID”



TERMINOLOGY

LONG HAULERS

LONG COVID

POST COVID SYNDROME

POST-ACUTE SEQUELAE OF SARS-CoV-2 INFECTION (PASC)

SYMPTOMS AND SYSTEMS

Acute Complications of COVID-19

Neuropsychiatric
- Cerebrovascular accident
- Large vessel disease
- Encephalopathy, delirium
- Anosmia, ageusia

Respiratory
- Pneumonia
- Hypoxemic respiratory failure, ARDS

Cardiovascular
- Arrhythmia
- Myocarditis

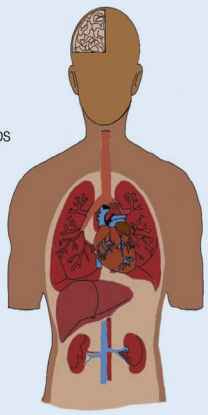
Hematologic, Vascular
- Coagulopathy
- Thrombotic events

Renal
- Acute kidney injury

Gastrointestinal, Hepatobiliary
- Diarrhea
- Acute liver injury

Musculoskeletal
- Rhabdomyolysis

Dermatologic
- Livedo reticularis
- Maculopapular or urticarial rash



Post-COVID Symptoms, Sequelae

Neuropsychiatric
- Neurocognitive deficits
- Mood changes
- Sensory & motor deficits
- Chronic fatigue and sleep disruption

Respiratory
- Persistent dyspnea
- Chronic cough

Cardiovascular
- Chest pain
- Palpitations

Hematologic, Vascular
- Persistent or recurrent thrombosis

Renal
- Chronic kidney disease

Gastrointestinal, Hepatobiliary
- Persistent liver dysfunction

Musculoskeletal
- Muscle wasting
- Weakness
- Deconditioning

Dermatologic
- Hair loss

Chest. Volume 159, Issue 3, March 2021, Pages 949-958

NEUROPSYCHIATRIC PRESENTATION

- Headaches
- Sleep disturbances – "COVID somnia"
- Anosmia, Phantosmia, Dysguesia
- Neurocognitive deficits - "Brain fog"
- Fatigue
- POTS
- Paresthesias – Small fiber neuropathy
- Anxiety
- Mood changes
- Functional neurological disorders

INCIDENCE AND PREVALENCE

- Not well defined – too early
- Definition of "post-acute" varies
- Varies based on different cohorts

UNIVERSITY OF WASHINGTON COHORT

JAMA Network Open

Research Letter | Infectious Diseases

Sequelae in Adults at 6 Months After COVID-19 Infection

Jennifer K. Logue, BS; Nicholas M. Franko, BS; Denise J. McCulloch, MD, MPH; Dylan McDonald, BA; Ariana Magedson, BS; Caitlin R. Wolf, BS; Helen Y. Chu, MD, MPH

UNIVERSITY OF WASHINGTON COHORT

- Location: Univ of Washington, Seattle
- Population: Adult patients diagnosed with COVID-19 were contacted between August and November 2020
- Follow-up interval: Between 3 and 9 months after disease onset
- Follow-up frequency: Once
- Follow-up method: Standardized questionnaire
- n: 177

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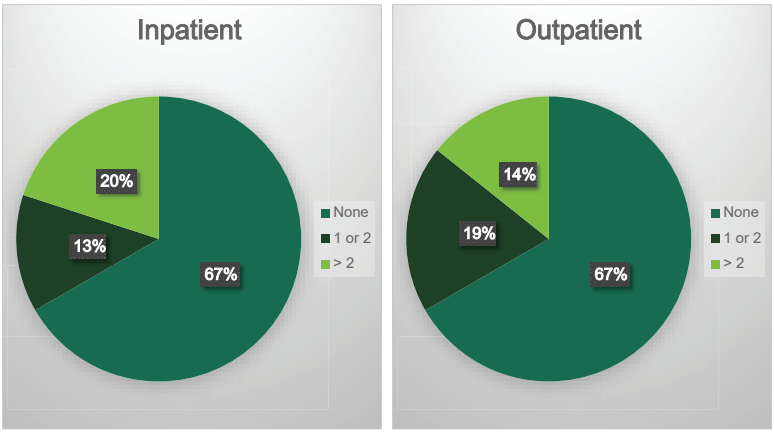
Persistent symptoms by initial severity



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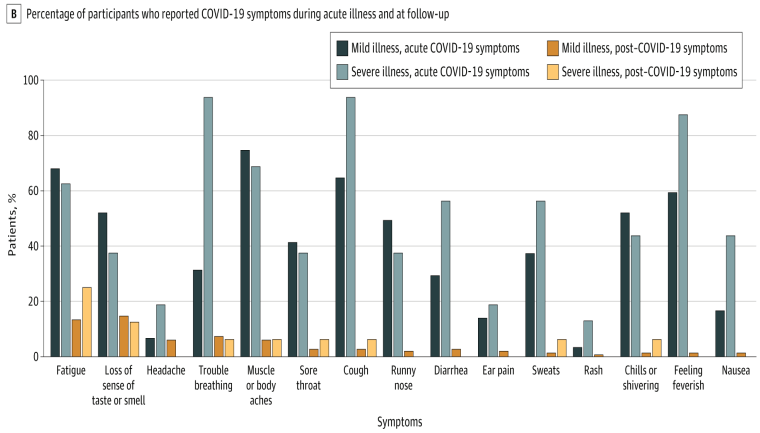
Persistent symptoms



MICHIGAN COHORT

- Location: Michigan, USA
- Population: Discharged between 16 March and 1 July 2020 from 38 participating hospitals
- Follow-up interval: 60 days
- Follow-up frequency: Once
- Follow-up type : Phone interview
- n: 1250 (only 488 completed phone survey)

Chopra V, Flanders SA, O'Malley M, Malani AN, Prescott HC. Sixty-Day Outcomes Among Patients Hospitalized With COVID-19. *Ann Intern Med.* 2021;174(4):576-578

MICHIGAN COHORT

- Post COVID Symptoms

	Number
Cardiopulmonary symptoms	159 /488 (33%)
Emotional/ Mental health problems	238/488 (49%)
New or worsening difficulty with ADL	58 /488 (12%)
Unable to return to work	78/195 (40%)
Required reduced work hour	30/117 (26%)

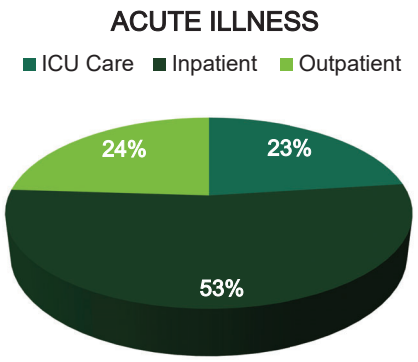
Chopra V, Flanders SA, O'Malley M, Malani AN, Prescott HC. Sixty-Day Outcomes Among Patients Hospitalized With COVID-19. *Ann Intern Med.* 2021;174(4):576-578

AUSTRIAN COHORT

- Location: 3 hospitals in Austria
- Population: Inpatient or outpatient COVID-19 diagnosis.
- Follow-up interval: 90 days after disease onset
- Follow-up frequency: Once, assessed between April and September 2020
- Follow-up type : In-person evaluation with structured interview, examination, MoCA, Sniffin' Sticks test, Questionnaires for QoL, anxiety, PTSD, fatigue
- n: 135

Rass V et al. Eur J Neurol March 2021

AUSTRIAN COHORT



RassV et al. Eur J Neurol March 2021

AUSTRIAN COHORT

NEUROLOGICAL SIGNS AND SYMPTOMS 3 MOS AFTER

- Hyposmia/Anosmia: 17% (44% in acute phase)
- Headache: 5% (29% in acute phase)
- Myalgia: 11%
- Gait abnormality: 5%
- Tremors: 10%
- Bradykinesia: 5%

RassV et al. Eur J Neurol March 2021

AUSTRIAN COHORT

COGNITION, MENTAL HEALTH, QoL 3 MOS AFTER

- MoCA < 26/30: 23% (29% in severe COVID-19, 30% in moderate, 3% in mild)
- Sleep disturbances: 34%
- Fatigue: 27%
- PTSD: 11%
- Depression: 11%
- Anxiety: 25%
- QoL impairment (SF-36): 31%

RassV et al. Eur J Neurol March 2021

NON-HOSPITALIZED COVID-19 "LONG HAULERS"

- Neuro -Covid-19 clinic of Northwestern Memorial Hospital, Chicago, IL
- 100 Non hospitalized patients prospective
  - 50 RT-PCR positive
- Mean age was 43.2± 11.3 years
- 70% were female

Graham E et al. Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 "long haulers". Ann Clin Transl Neurol, 8: 10731085

NON-HOSPITALIZED COVID-19 "LONG HAULERS"

The main neurologic manifestations were:

- "Brain fog": 81%
- Headache: 68%
- Numbness/tingling: 60%
- Dysgeusia: 59%
- Anosmia: 55%
- Myalgias (55%),
- Fatigue: 85%

Graham E et al. Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 "long haulers". Ann Clin Transl Neurol, 8: 10731085

EClinicalMedicine 25 (2020) 100484

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

Research Paper

Cerebral Micro-Structural Changes in COVID-19 Patients – An MRI-based 3-month Follow-up Study

Yiping Lu, MD[a,1], Xuanxuan Li, MD[a,1], Daoying Geng, MD, Prof[a,1], Nan Mei, MD[a,1], Pu-Yeh Wu, PhD[b], Chu-Chung Huang, PhD[c], Tianye Jia, PhD[d], Yajing Zhao, MD[a], Dongdong Wang, MD[a], Anling Xiao, MD, Prof[a,**], Bo Yin, PhD, Prof[a,*]

DTI IN COVID-19 SURVIVORS

- 60 recovered COVID-19 patients and 39 controls
- 55% had neurological symptoms at follow up (approx 90 days after onset of initial symptoms)
- Statistically significant higher bilateral gray matter volumes (GMV) in olfactory cortices, hippocampi, insulas, left Rolandic operculum, left Heschl's gyrus and right cingulate gyrus
- Lower diffusivity parameters (MD, AD, RD) and higher FA values were recognized in the white matter from COVID-19 cohort

CASE

- 47 yo F with fever, anosmia, ageusia, sore throat. COVID-19 diagnosed based on positive RT-PCR
- Within few days developed lightheadedness, palpitations, hyperhidrosis and tremulousness
- She had intermittent tingling, burning in feet prior to COVID-19; this was now more persistent
- Autonomic reflex screen performed 8 months into her symptoms
  - HR responses to deep breathing and VM were normal
  - Quantitative Sudomotor Axonal Reflex Testing: reduced sweat outputs in the forearm and foot
  - She developed palpitations and worsening headache during the 10-minute head-up tilt table (HUT) test. Her heart rate went up from 81 bpm at baseline to a maximum of 128 bpm, and 103 bpm on average during the period of tilt.
- Diagnosis: Sympathetic adrenergic and cholinergic impairment and Orthostatic Intolerance
- Skin punch biopsy: normal epidermal nerve fiber density

DYSAUTONOMIA AND COVID-19

- Orthostatic hypotension
- POTS
- COMPASS-31 Questionnaire to post COVID patients in clinic from 4 weeks to 9 months, orthostatic VS measured
- n= 180
- OH found in 13.8%
- Median COMPASS-31 score was 17.6
- Higher in females

Stella A et al. Autonomic dysfunction in post-COVID patients with and without neurological symptoms: a prospective multidomain observational study. J Neurol. 2021 Aug 12 :-10.

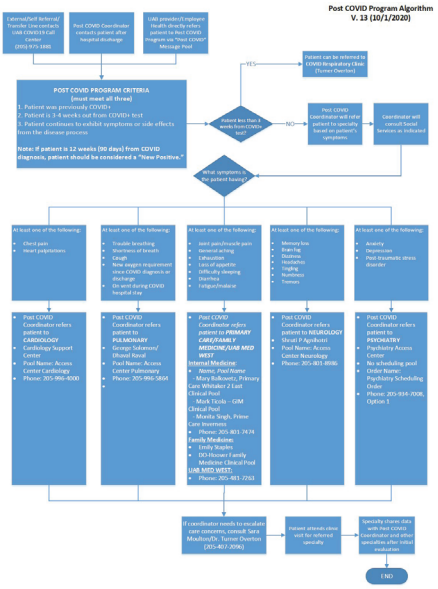
COVID-19 AND NEURODEGENERATIVE DISEASES

- Acute Parkinsonism
- CJD
- Acceleration of Dementia
- Unmasking of Dementia
- Role in development of Dementia is unclear

SUMMARY

- Early symptoms: Headache, anosmia, ageusia, dizziness
- Neurologic complications in severe COVID-19 includes encephalopathy, strokes, seizures, leukoencephalopathy
- Viral encephalitis is extremely rare
- Post and para-infectious complications include GBS, Transverse myelitis, ADEM
- Post-acute COVID-19 syndrome is associated with fatigue, cognitive changes, dysautonomia
- Long term sequalae of COVID-19 and its role in neurodegenerative diseases is unknown

POST- COVID PROGRAM AT UAB



UAB POST-COVID PROGRAM

- Criteria: Previously COVID +ve, >3weeks out from date of test, continues to have symptoms
- Post COVID coordinator will call patient and refer to dedicated Post-COVID specialists based on symptoms
- General Internal Medicine, Family medicine, Cardiology, Pulmonology, Neurology, Psychiatry, Ophthalmology, ENT

THANK YOU

- Questions or comments?

- Email: sagnih@uab.edu