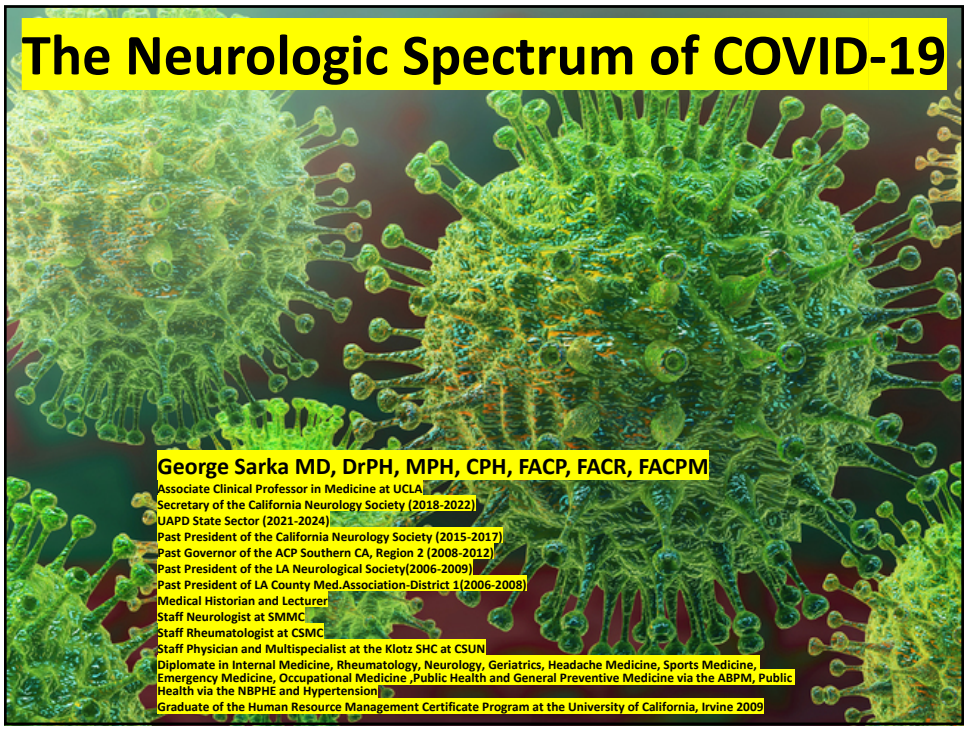


Objectives

1. Describe the protean neurological presentations and long-haul sequelae of COVID-19 infections.
2. Discuss the evaluation/treatment of Covid-19 from a neurological point-of-view.

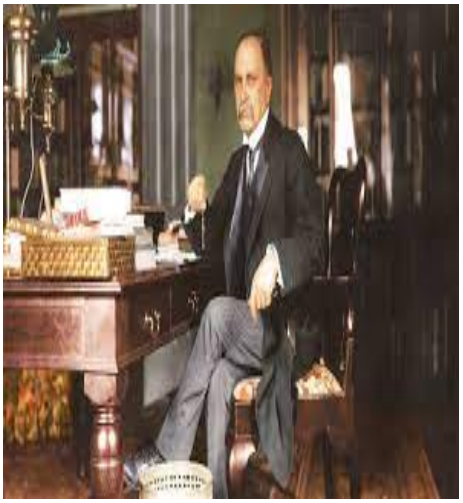
Financial Disclosures

1. **Faculty Disclosure**: George Sarka MD, DrPH, MPH, Associate Clinical Professor in Medicine at UCLA, has received financial compensation for Speakers' Bureau from Abbvie.
2. All relevant financial relationships have been mitigated.
3. Will not discuss unlabeled/investigational uses of a commercial product

Introduction

- *"Humanity has but three great enemies: fever, famine, and war; of these by far the greatest, by far the most terrible, is fever."*

  Sir William Osler, 1896



Epidemiology for Neurologic Complications of COVID-19

- Neurologic complications are common in hospitalized COVID-19 patients.
- >80% of hospitalized COVID patients may have neurologic symptoms during the course of their disease.
- Myalgias, Headaches, Encephalopathy and Dizziness are most common, occurring in about a third of patients from China, Europe and the US studies below.
- Stroke, Movement Disorders, Motor and Sensory Deficits, Ataxia and Sz are less common.
- Critically ill patients have a higher proportion of neurologic complications that those with less severe illness.

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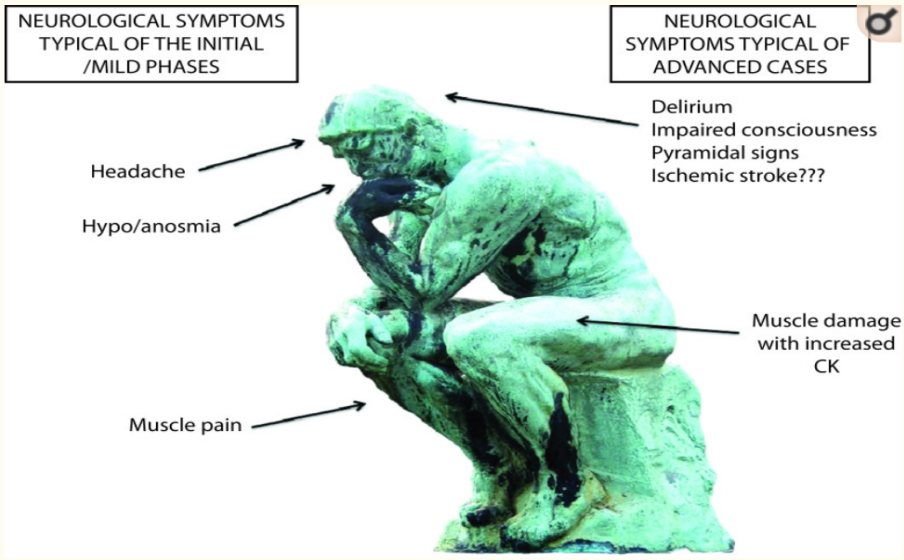

Figure 2

The most typical neurological features associated with mild (left) and severe (right) coronavirus disease 2019.

Source: Orsucci, D et al., Neurological features of COVID-19 and their treatment: a review, *Drugs in Context* 2020; 9:2020-5-1.

Review > Rev Neurol (Paris). Jan-Feb 2021;177(1-2):51-64. doi: 10.1016/j.neurol.2020.10.001. Epub 2020 Dec 16.

Neurological manifestations associated with SARS-CoV-2 and other coronaviruses: A narrative review for clinicians

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Affiliations + expand

PMID: 33446327 PMCID: PMC7832485 DOI: 10.1016/j.neurol.2020.10.001

Free PMC article

Abstract

Introduction: The past two decades have been marked by three epidemics linked to emerging coronaviruses. The COVID-19 pandemic highlighted the existence of neurological manifestations associated with SARS-CoV-2 infection and raised the question of the neuropathogenicity of coronaviruses. The aim of this review was to summarize the current data about neurological manifestations and diseases linked to human coronaviruses.

Material and methods: Articles have been identified by searches of PubMed and Google scholar up to September 25, 2020, using a combination of coronavirus and neurology search terms and adding relevant references in the articles.

Results: We found five cohorts providing prevalence data of neurological symptoms among a total of 2533 hospitalized COVID-19 patients, and articles focusing on COVID-19 patients with neurological manifestations including a total of 580 patients. Neurological symptoms involved up to 73% of COVID-19 hospitalized patients, and were mostly headache, myalgias and impaired consciousness. Central nervous system (CNS) manifestations reported in COVID-19 were mostly non-specific encephalopathies that represented between 13% and 40% of all neurological manifestations; post-infectious syndromes including acute demyelinating encephalomyelitis (ADEM, n=13), acute necrotizing encephalopathy (ANE, n=4), Bickerstaff's encephalitis (n=5), generalized myoclonus (n=3) and acute transverse myelitis (n=7); other encephalitis including limbic encephalitis (n=9) and miscellaneous encephalitis with variable radiologic findings (n=26); acute cerebrovascular diseases including ischemic strokes (between 1.3% and 4.7% of COVID-19 patients), hemorrhagic strokes

Table 1

Prevalence and characteristics of neurological manifestations in COVID-19 patients: data from eight cohort studies.

Authors	Mao et al.	Romero-Sanchez et al.	Mahammedi et al.	Guilmot et al.	Agarwal et al.	Varatharaj et al.	Kremer et al.	Paterson et al.	Meppiel et al.
Setting	China, 3 centers	Spain, 2 centers	Italy, 3 centers	Belgium, 3 centers	USA, 1 center	UK-wide surveillance study	France, 11 centers	UK, 1 center	France, 46 centers
COVID-19 patients, total *n* (%)	214 (100)	841 (100)	725 (100)	349 (100)	404 (100)	–	–	–	–
COVID-19 patients with neurological symptoms, *n* (%)	78 (36.4)	483 (57.4)	108 (14.9)	15 (4.3)	295 (73.0)	153	64	43	222
Headache	28 (13.1)	119 (14.1)	13 (1.8)	–	82 (20.3)	–	10	–	24
Dizziness	36 (16.8)	51 (6.1)	4 (0.6)	–	31 (7.7)	–	–	–	5
Altered mental status and/or impaired consciousness	16 (7.5)	165 (19.6)	64 (8.8)	7 (1.5)	86 (21.3)	39	34	–	117
Ataxia	1 (0.5)	–	2 (0.3)	–	20 (5.0)	–	–	–	–
Seizure	1 (0.5)	6 (0.7)	1 (0.1)	2 (0.6)	2 (0.5)	-	2	1	21
Anosmia	12 (5.6)	41 (4.9)	2 (0.3)	2 (0.6)	18 (4.5)	1	1	-	7
Nerve pain	5 (2.3)	–	3 (0.4)	–		–	–	–	–
Dysautonomia	–	21 (2.5)	–	–	1 (0.2)	–	–	–	–
Neuropsychiatric	–	167 (19.8)	–	3 (0.9)		–	–	–	–
Myalgia	23 (10.7)	145 (17.2)	13 (1.8)	–	131 (32.4)	23	–	–	–
Neurological manifestations, *n* (%)									
Acute cerebrovascular disease	6 (2.8)	14 (1.7)	42 (5.8)	3 (0.9)	3 (0.7)	77	–	–	57
Ischemic stroke	–	11 (1.3)	34 (4.7)	2 (0.6)	2 (0.5)	57	17	8	52
Hemorrhagic stroke	–	–	6 (0.8)	1 (0.3)	1 (0.3)	9	–	–	5
Cerebral Venous Thrombosis	–	–	2 (0.3)	0	0	2	–	–	1
Posterior reversible encephalopathy	–	1 (0.1)	1 (0.1)	0	0	–	–	–	0
Encephalopathy/encephalitis	–	1 (0.1)	4 (0.6)[a]	10 (2.9)[c]	86 (21.3)	16	19[e]	21[f]	88[g]
Myelitis	–	–	–	–	–	–	–	–	0
Guillain–Barré syndrome and variants	–	1 (0.1)	3 (0.4)[b]	1 (0.3)[d]	0	4	–	7	15[h]
Isolated oculomotor neuropathy	–	–	–	1 (0.3)	0	–	–	1	2

Source: https://pubmed.ncbi.nlm.nih.gov/33446327/

Guerrero et al. BMC Infectious Diseases (2021) 21:515
https://doi.org/10.1186/s12879-021-06185-6

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Central and peripheral nervous system involvement by COVID-19: a systematic review of the pathophysiology, clinical manifestations, neuropathology, neuroimaging, electrophysiology, and cerebrospinal fluid findings

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Abstract

Background: SARS-CoV-2 can affect the human brain and other neurological structures. An increasing number of publications report neurological manifestations in patients with COVID-19. However, no studies have comprehensively reviewed the clinical and paraclinical characteristics of the central and peripheral nervous system's involvement in these patients. This study aimed to describe the features of the central and peripheral nervous system involvement by COVID-19 in terms of pathophysiology, clinical manifestations, neuropathology, neuroimaging, electrophysiology, and cerebrospinal fluid findings.

Methods: We conducted a comprehensive systematic review of all the original studies reporting patients with neurological involvement by COVID-19, from December 2019 to June 2020, without language restriction. We excluded studies with animal subjects, studies not related to the nervous system, and opinion articles. Data analysis combined descriptive measures, frequency measures, central tendency measures, and dispersion measures for all studies reporting neurological conditions and abnormal ancillary tests in patients with confirmed COVID-19.

Results: A total of 143 observational and descriptive studies reported central and peripheral nervous system involvement by COVID-19 in 10,723 patients. Fifty-one studies described pathophysiologic mechanisms of neurological involvement by COVID-19, 119 focused on clinical manifestations, 4 described neuropathology findings, 62 described neuroimaging findings, 28 electrophysiology findings, and 60 studies reported cerebrospinal fluid results. The reviewed studies reflect a significant prevalence of the nervous system's involvement in patients with COVID-19, ranging from 22.5 to 36.4% among different studies, without mortality rates explicitly associated with neurological involvement by SARS-CoV-2. We thoroughly describe the clinical and paraclinical characteristics of neurological involvement in these patients.

Conclusions: Our evidence synthesis led to a categorical analysis of the central and peripheral neurological involvement by COVID-19 and provided a comprehensive explanation of the reported pathophysiological mechanisms by which SARS-CoV-2 infection may cause neurological impairment. International collaborative efforts and exhaustive neurological registries will enhance the translational knowledge of COVID-19's central and peripheral neurological involvement and generate therapeutic decision-making strategies.

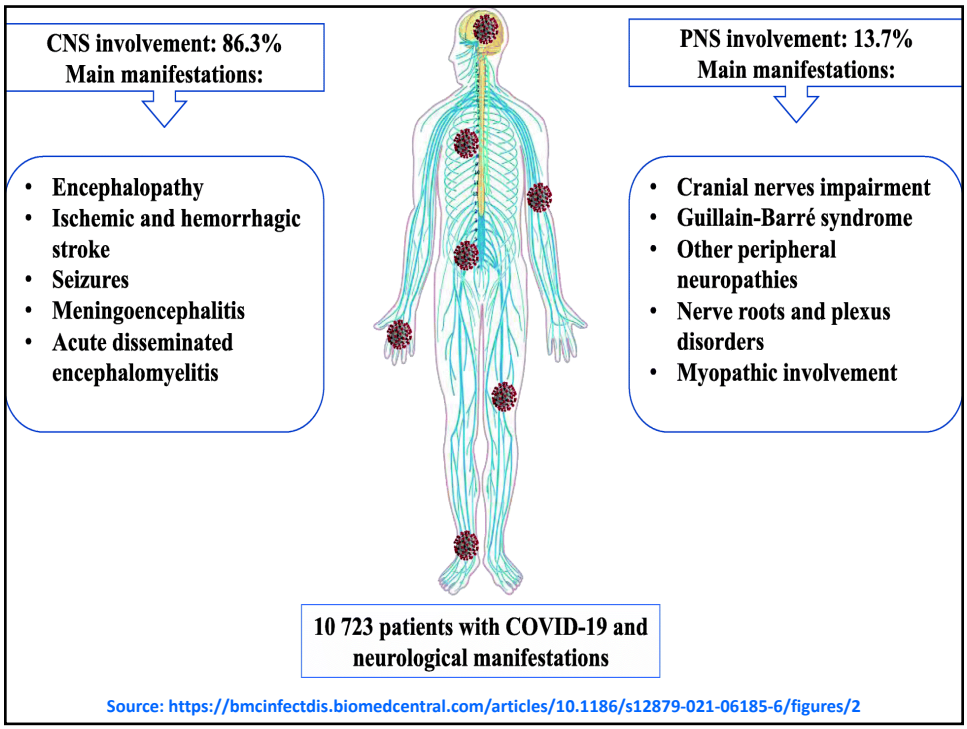

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Table 1 Neurological conditions associated with COVID-19

Clinical conditions associated with COVID-19 affecting the central nervous system	**No. of patients / Proportion**
Encephalopathy	990 (60·7%)
Unspecified stroke type	416 (25·5%)
Ischemic stroke	159 (9·7%)
Hemorrhagic stroke	40 (2·4%)
Encephalitis and meningoencephalitis	19 (1·2%)
Acute disseminated encephalomyelitis (ADEM)	4 (0·2%)
Venous sinus thrombosis	3 (0·2%)
Multiple sclerosis exacerbation	2 (0·1%)
Total	1633 (100%)
Clinical conditions associated with COVID-19 affecting the peripheral nervous system	**No. of patients / Proportion**
Guillain-Barré syndrome	22 (51·2%)
Other cranial nerve disorders	12 (27·9%)
Facial palsy (Bell syndrome)	5 (11·6%)
Miller-Fisher syndrome and polyneuritis cranialis	4 (9·3%)
Total	43 (100%)

Source: https://bmcinfectdis.biomedcentral.com/track/pdf/10.1186/s12879-021-06185-6.pdf

Table 2 Distribution of signs and symptoms indicating central nervous system involvement in patients with COVID-19

Signs and symptoms indicating central nervous system involvement	No. of patients / Proportion
Diffuse compromise	**8129 (91·5%)**
Psychiatric symptoms (including anxiety disorders, mood disorders, psychosis, and insomnia)	4981
Headache	1805
Dizziness	527
Consciousness impairment	416
Delirium	340
Nausea/vomiting	16
Nuchal rigidity	4
Non-specific combination of signs and symptoms	40
Focal deficit	**410 (4·6%)**
Extrapyramidal disorders	279
Corticospinal tract impairment	61
Ataxia	18
Dysarthria	13
Amnesia	12
Aphasia	7
Monoparesis	6
Central facial weakness	5
Myoclonus	5
Homonymous hemianopia	4
Seizures	**346 (3·9%)**
Non-specified seizures	324
Generalized seizures	9
Non-convulsive status epilepticus	6
Focal seizures	3
Seizure-like events (abnormal involuntary movements)	3
Non-epileptic convulsive syncope	1
Total patients with CNS signs and symptoms	**8885 (100%)**

Source: https://bmcinfectdis.biomedcentral.com/track/pdf/10.1186/s12879-021-06185-6.pdf

Table 3 Distribution of signs and symptoms indicating peripheral nervous system involvement in patients with COVID-19

Signs and symptoms indicating peripheral nervous system involvement	No. of patients / Proportion
Smell/taste impairment	**746 (52·8%)**
Anosmia and ageusia	477
Anosmia/hyposmia	128
Ageusia/dysgeusia	141
Visual impairment	**9 (0·6%)**
Unspecified decreased visual acuity	8
Complete visual loss	1
Oculomotor impairment	**14 (1%)**
Ophthalmoparesis	7
Diplopia	3
Anisocoria	1
Bilateral mydriasis	1
Bilateral abducens palsy	1
Unilateral abducens palsy	1
Facial palsy	**13 (0·9%)**
Bilateral weakness/diplegia	7
Unilateral	6
Other cranial nerve impairment	**32 (2·3%)**
Glossopharyngeal neuralgia	9
Trigeminal neuralgia	8
Tinnitus	5
Decreased hearing	5
Vasoglossopharyngeal neuralgia	2
Dysphagia	2
Reduced tongue movements/tongue deviation	1
Peripheral neuropathies involving trunk and limbs	**353 (24·9%)**
Mixed neuropathy	247
Pure sensitive impairment	31
Paresthesia	30
Hypoesthesia	1
Pure motor impairment	40
Areflexia	14
Distal weakness	8
Tetraparesis	7
Gait difficulties/instability	6
Paraparesis	3
Tetraplegia	1
Paraplegia	1
Neuralgia	8
Limb neuralgia	7
Occipital neuralgia	1

Source: https://bmcinfectdis.biomedcentral.com/track/pdf/10.1186/s12879-021-06185-6.pdf

Table 3 Distribution of signs and symptoms indicating peripheral nervous system involvement in patients with COVID-19 *(Continued)*

Signs and symptoms indicating peripheral nervous system involvement	No. of patients / Proportion
Dysautonomia manifestations	27
Nerve roots and plexus disorders	145 (10·3%)
Myopathic involvement	102 (7·2%)
Total patients with PNS signs and symptoms	1414 (100%)

Source: https://bmcinfectdis.biomedcentral.com/track/pdf/10.1186/s12879-021-06185-6.pdf

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Neurological issues in children with COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19) usually leads to a mild infectious disease course in children, but serious complications may occur in conjunction with both acute infection and associated phenomena such as the multisystem inflammatory syndrome in children (MIS-C). Neurological symptoms, which have been predominantly reported in adults, range from mild headache to seizure, peripheral neuropathy, stroke, demyelinating disorders, and encephalopathy. Similar to respiratory and cardiac manifestations of COVID-19, neurological complications present differently based on age and underlying comorbidities. This review provides a concise overview of the neurological conditions seen in the context of COVID-19, as well as potential mechanisms and long-term implications of COVID-19 in the pediatric population from literature reviews and primary data collected at NewYork-Presbyterian Morgan Stanley Children's Hospital.

1. Clinical observations in children

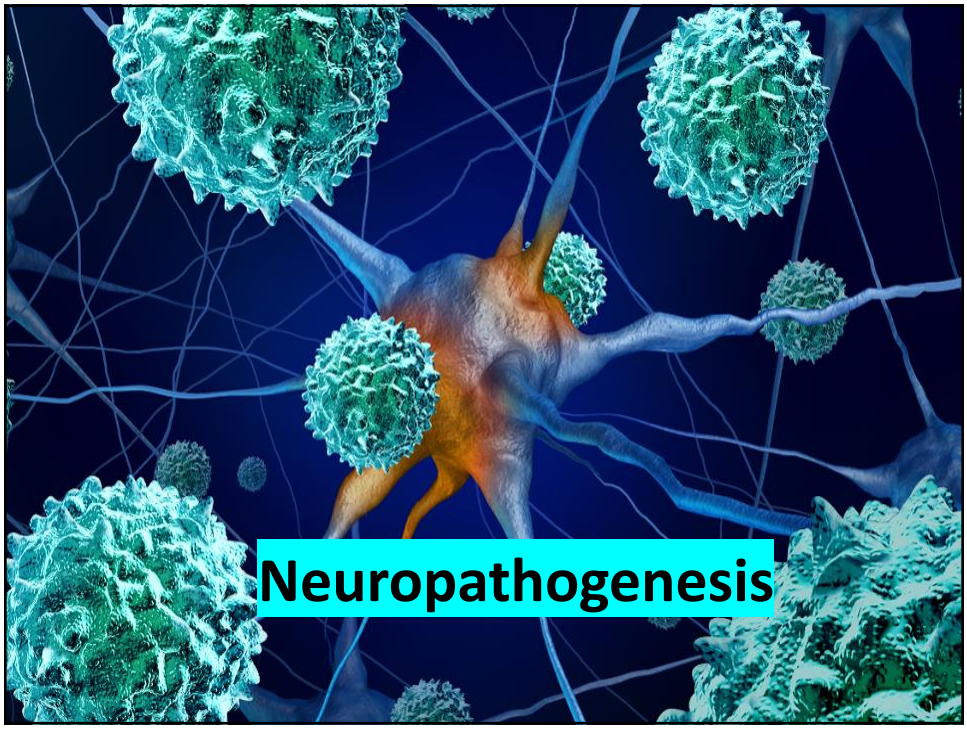
The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, causing coronavirus disease 2019 (COVID-19), has affected more than 30 million people worldwide [1]. More than 6 million cases have been reported in the United States as of September 2020 [1], with children comprising 8.4 % of reported cases [2]. Although respiratory symptoms and multisystem inflammatory syndrome in children (MIS-C) have predominated in both scientific and lay literature, neurological phenomena have also been associated with COVID-19. 28 % of pediatric COVID-19 patients in the United States experienced headaches [3]. Among children diagnosed with MIS-C in New York, 31–47 % experienced neurological symptoms, including headache, altered mental status, and encephalopathy [4,5]. Moreover, a multicenter study of children diagnosed with MIS-C across the United States found that 5 % suffered severe neurological complications, such as seizure, coma, encephalitis, demyelinating disorders, and aseptic meningitis [6]. In the United Kingdom, of 27 children with MIS-C, 4 had new-onset neurological symptoms, including encephalopathy, dysarthria, dysphagia, cerebellar ataxia, and peripheral neuropathy leading to global proximal muscle weakness and reduced reflexes [7]. These children were between 8 and 15 years old, all had MRI or CT changes involving the splenium of the corpus callosum, and all presented with fever, shock, and rash. Reversible lesions of the corpus callosum have been observed in Kawasaki disease [8,9], as well as in other viral and inflammatory encephalopathies [10,11]. However, this UK case series did not include detailed information regarding the metabolic derangements experienced by these patients, which makes it somewhat challenging to interpret some of the more non-specific neurological symptoms, such as headache or fatigue (Fig. 1).

Encephalopathy has also been noted in infants and toddlers with COVID-19. Four out of five children younger than 3 months with positive nasal swabs for SARS-CoV-2 in a UK COVID-19 unit presented with axial hypotonia, drowsiness, or moaning. All five children had normal CSF studies, including cell counts, glucose and PCR for SARS-CoV-2, and were discharged within 3 days after rapid improvement [12]. At our own institution, a 6-week-old infant presented with one day of cough, fever, and 10-second episodes of leg stiffening with upward gaze deviation. Other than nasopharyngeal PCR swab positive for SARS-CoV-2 and an EEG showing temporal sharp waves and vertex delta slowing,

The most common neurological symptoms in children included

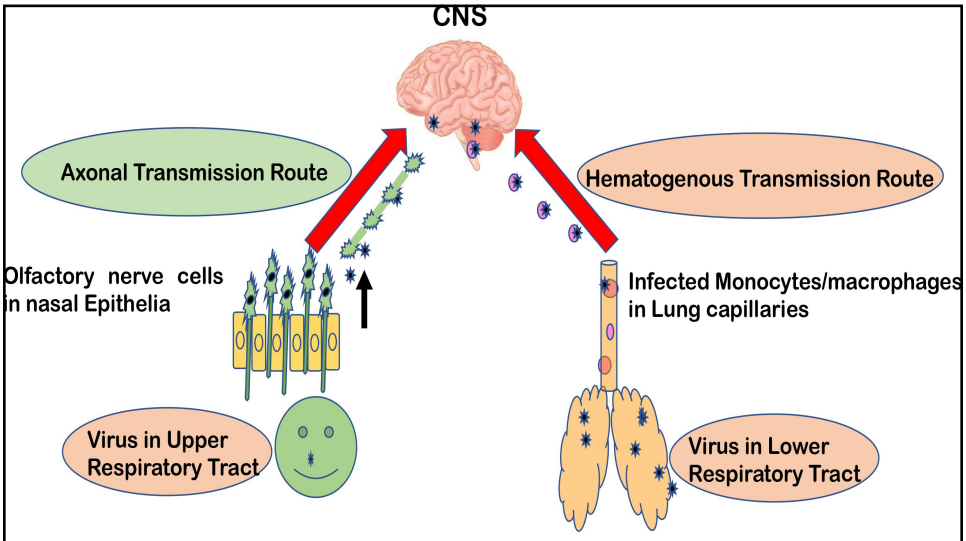
- Headache (n = 12, 34 %)
- Fatigue or malaise (n = 9, 25 %),
- Altered Mental Status (n = 8, 23 %),
- Weakness (n = 5, 14 %), and
- Seizure (n = 4, 11 %).
- Of note, 3 patients presented with Cranial Nerve VI palsy and 2 of these patients also had Intracranial Hypertension.
- Only 2 patients reported Dysgeusia or Ageusia and only 1 patient suffered from a Stroke.
- It should be noted that the median patient age was 9 years

Source: https://www.spo-dz.com/wp-content/uploads/2021/01/Neurological-issues-in-children-with-COVID-19.pdf



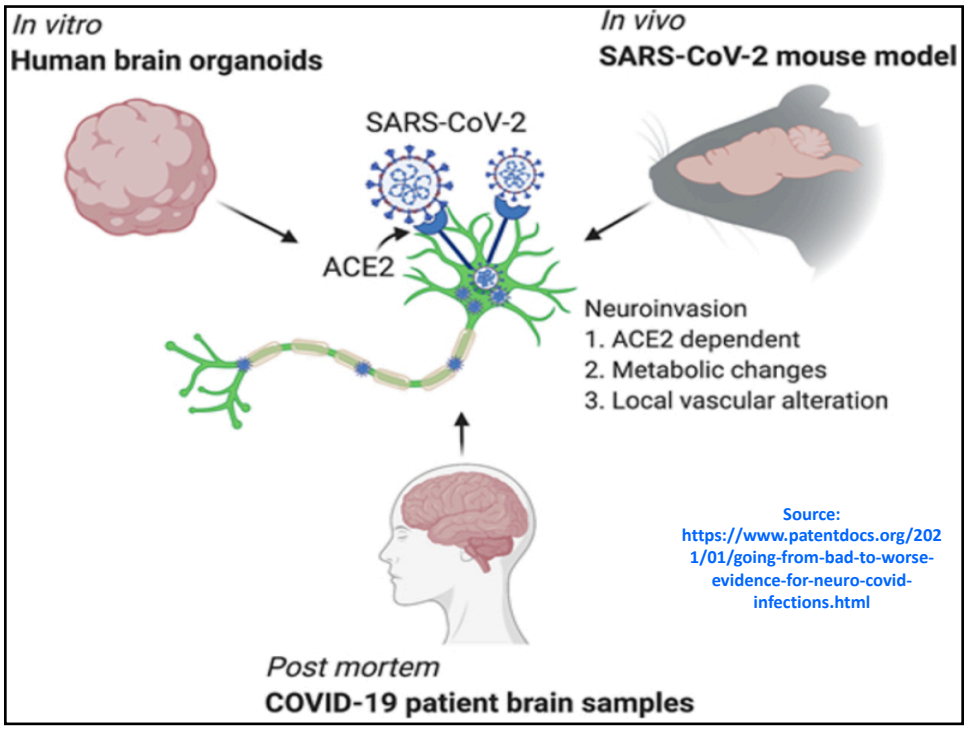
Virus name	Major route to enter CNS	References
Human Coronaviruses (HCoV)	Olfactory receptor neurons, Hematogenous route	PMID:16036791
		PMID:32167747
Influenza Virus (IAV)	Olfactory route	PMID:24550441
Respiratory syncytial Virus (RSV)	Olfactory receptor neurons, Olfactory bulb	PMID:31861926
Nipah Virus (NiV)	olfactory epithelium through the cribriform plate into the olfactory bulb	PMID:23071900
Herpes Simplex Virus (HSV)	Trigeminal ganglia, through vomeronasal system, and the hematogenous **route**	PMID:30863282
Rabies Virus	Transport through nerve endings.	PMID:2016778
Polio Virus (PV)	After oral ingestion, enteric nerve pathway, crossing of BBB.	PMID:22529845
Measles Virus (MV)	Crossing of BBB via infecting endothelial cells	PMID:27483301
West Nile Virus	Axonal transport	PMID:17939996
Japanese Encephalitis Virus (JEV)	Hematogenous route	PMID:25762733
Dengue Virus (DENV)	Hematogenous route	PMID:31293558
Hendra Virus	Direct Neuronal Infection	PMID:30985897

Source: https://www.frontiersin.org/files/Articles/565521/fimmu-11-565521-HTML/image_m/fimmu-11-565521-t001.jpg

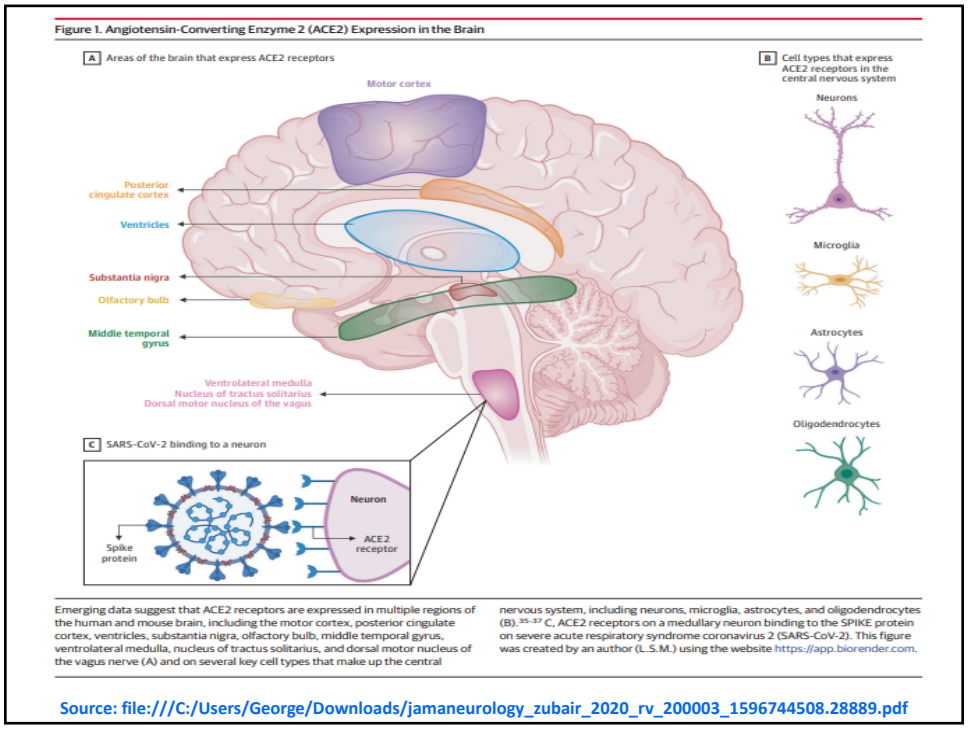


Major entry routes taken by viruses to reach the CNS. The schematic is describing two major transmission routes taken by viruses to reach the CNS: hematogenous transmission route and olfactory neuronal transport route. Respiratory viruses may infect the lower respiratory tract and lung epithelia, which are in close contact with fine blood capillaries for oxygen transport. Viruses travel toward the basolateral side of lung epithelia, enter the bloodstream, and eventually infect monocytes/macrophages in blood capillaries. As a "Trojan Horse" route, these infected monocytes can travel to the CNS. In the olfactory neuronal transmission route, viruses travel from one neuron to another via synaptic endings by using cell motor proteins to ultimately reach the CNS.

Source: https://www.frontiersin.org/articles/10.3389/fimmu.2020.565521/full



Source: https://www.patentdocs.org/2021/01/going-from-bad-to-worse-evidence-for-neuro-covid-infections.html



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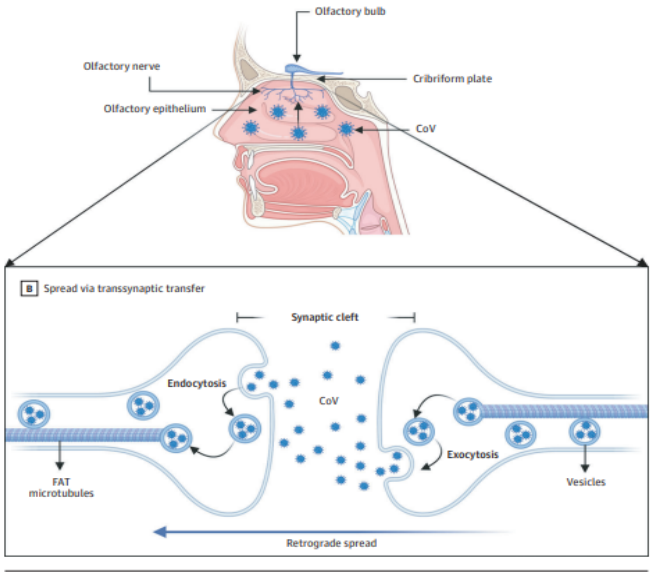

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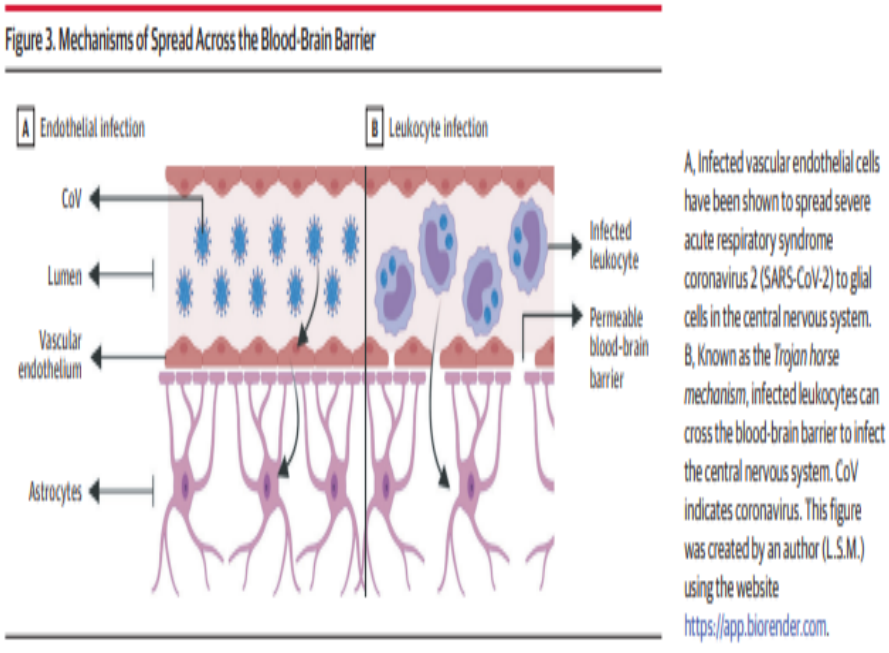

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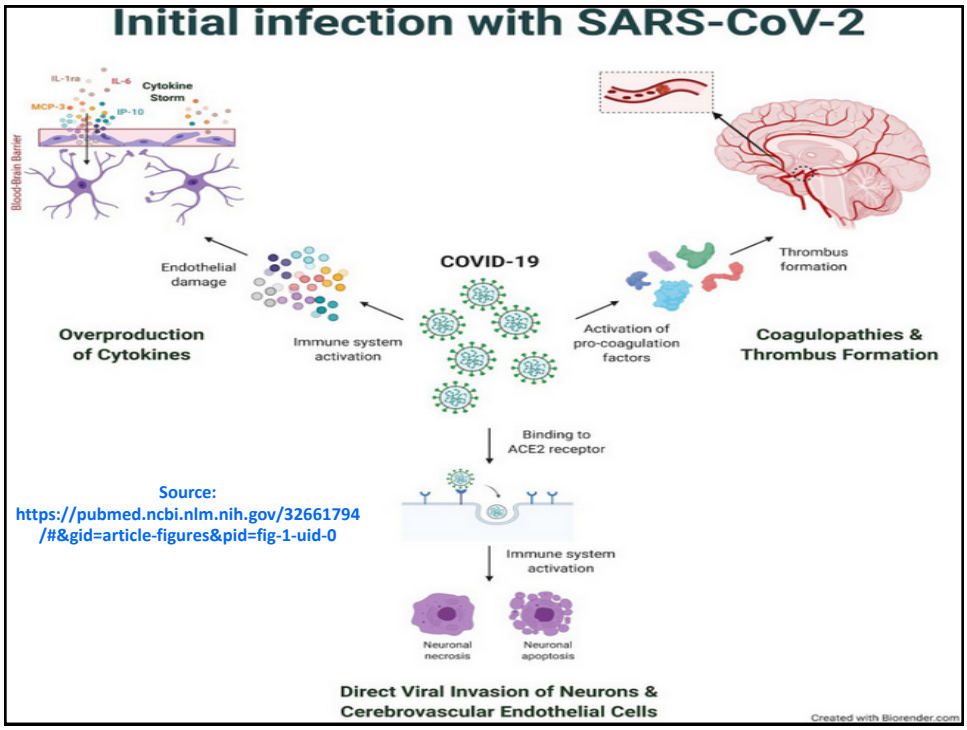

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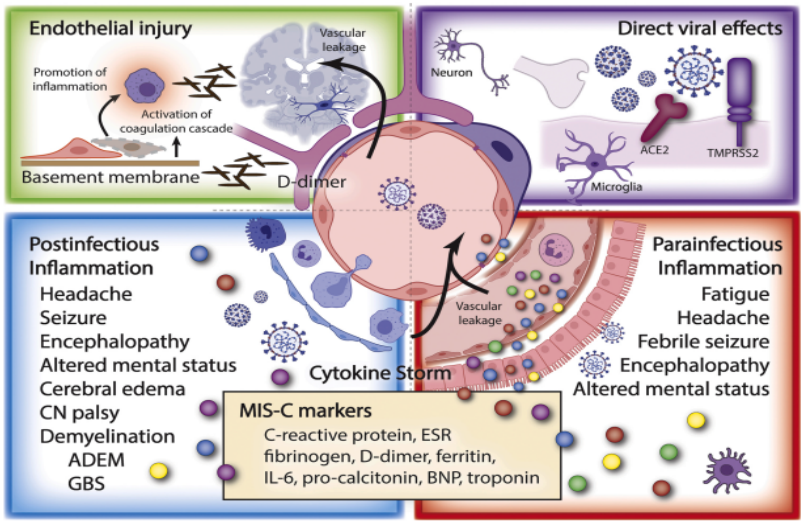
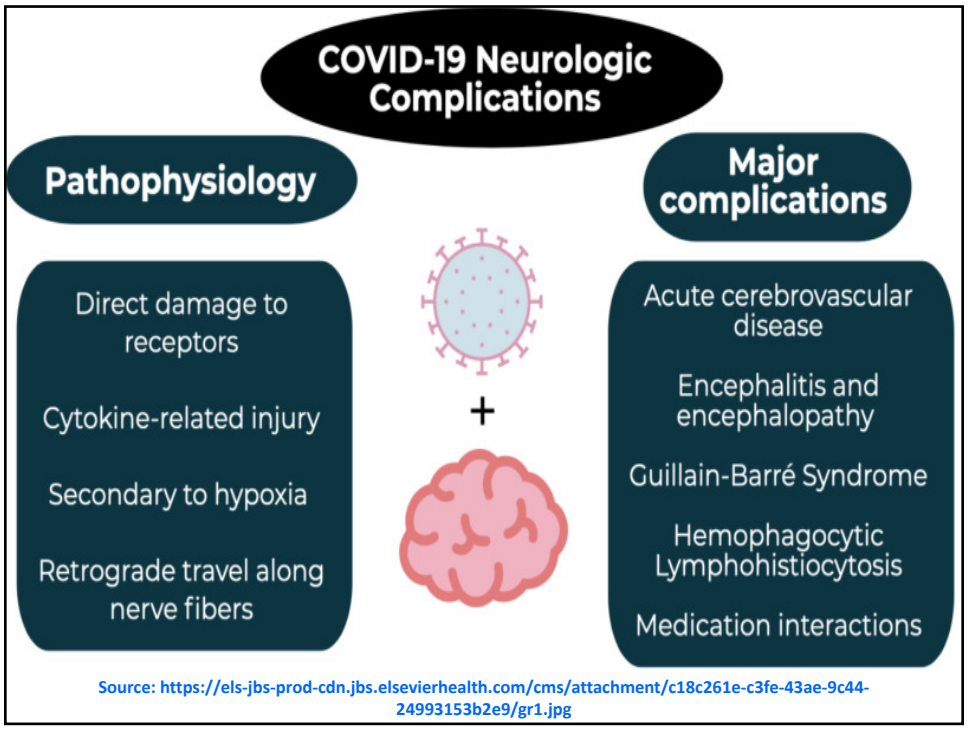


Fig. 1. Hypothesized mechanisms of COVID-19 neurological manifestations.
Direct viral effects upon the nervous system, endothelial injury, and downstream effects of para- and post-infectious inflammation, have each been proposed as potential etiologies of the neurological manifestations of Coronavirus disease 2019 (COVID-19). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may cross into the central nervous system (CNS) via a variety of mechanisms. Endothelial injury may precipitate thrombotic events, as well as release of virus and inflammatory mediators. Cytokine release due to pulmonary or systemic infection may instigate neurological sequelae. And, post-infectious inflammation induced by SARS-CoV-2 may trigger autoimmune phenomena, such as demyelinating disease and encephalopathy. The multisystem inflammatory syndrome in children associated with SARS-CoV-2 may represent a spectrum of para- and post-infectious complications, separate but similar to other inflammatory conditions in children known to sometimes present with neurological sequelae. ESR (erythrocyte sedimentation rate); BNP (B-type natriuretic peptide); IL-6 (interleukin 6).

Source: https://www.spo-dz.com/wp-content/uploads/2021/01/Neurological-issues-in-children-with-COVID-19.pdf



Source: https://els-jbs-prod-cdn.jbs.elsevierhealth.com/cms/attachment/c18c261e-c3fe-43ae-9c44-24993153b2e9/gr1.jpg

Neuropathogenesis

a) Neurologic Injury from Systemic Dysfunction
b) Renin-angiotensin System Dysfunction
c) Immune Dysfunction
    a) Proinflammatory State
    b) Para infectious and Pro infectious Triggers
d) Direct Viral Invasion of the Nervous System

a) Neurologic Injury from Systemic Dysfunction

- Hypoxemia—encephalopathy
- Metabolic derangements due to organ failure
  - Renal Impairment
  - Hepatic Impairment
  - Multiple Organ Failure
- Medication effects.

b) Renin-Angiotensin System Dysfunction (RAS)

- Maladaptive activity of the RAS
- SARS-CoV-2 utilizes ACE2, a membrane-bound protein, as its point of entry into cells.
  - ACE2 functions to convert angiotensin II into angiotensin which as vasodilator, antiproliferative and antifibrotic properties.
- SARS-CoV-2 virus via ACE2 may damage vascular endothelial cells by inhibiting mitochondrial function and endothelial nitric oxide synthetase activity.

c) Immune Dysfunction

- Proinflammatory State-critical ill patients may develop signs of severe systemic inflammation with cytokine release syndrome—causing fever, elevated inflammatory markers) and proinflammatory cytokines.
  - Confusions and AMS
  - Endotheliitis
  - Thromboinflammation
- Para-infectious and Post-infectious Triggers

Para-infectious Conditions

- Anecdotal reports of other diseases and conditions that may be triggered by the immune system response to COVID-19 include para-infectious conditions that occur within days to a few weeks after infection:
  - Multi-system inflammatory syndrome - which causes inflammation in the body's blood vessels
  - Transverse myelitis - an inflammation of the spinal cord
  - Guillain-Barré syndrome (sometimes known as acute polyradiculoneuritis) - a rare neurological disorder which can range from brief weakness to nearly devastating paralysis, leaving the person unable to breathe independently
  - Dysautonomia - dysfunction of the autonomic nerve system, which is involved with functions such a breathing, heart rate, and temperature control
  - Acute disseminating encephalomyelitis (ADEM) - an attack on the protective myelin covering of nerve fibers in the brain and spinal cord
  - Acute necrotizing hemorrhagic encephalopathy - a rare type of brain disease that causes lesions in certain parts of the brain and bleeding (hemorrhage) that can cause tissue death (necrosis)
  - Facial nerve palsies (lack of function of a facial nerve) such as Bell's Palsy
  - Parkinson's disease-like symptoms have been reported in a few individuals who had no family history or early signs of the disease

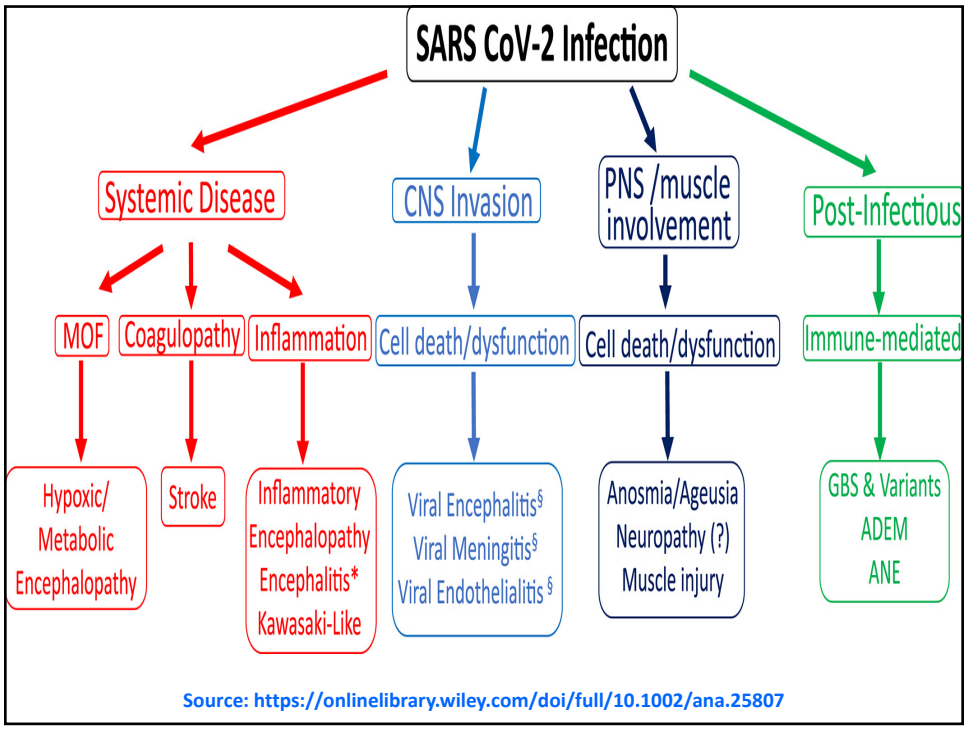
NEUROLOGICAL COMPLICATIONS OF COVID-19

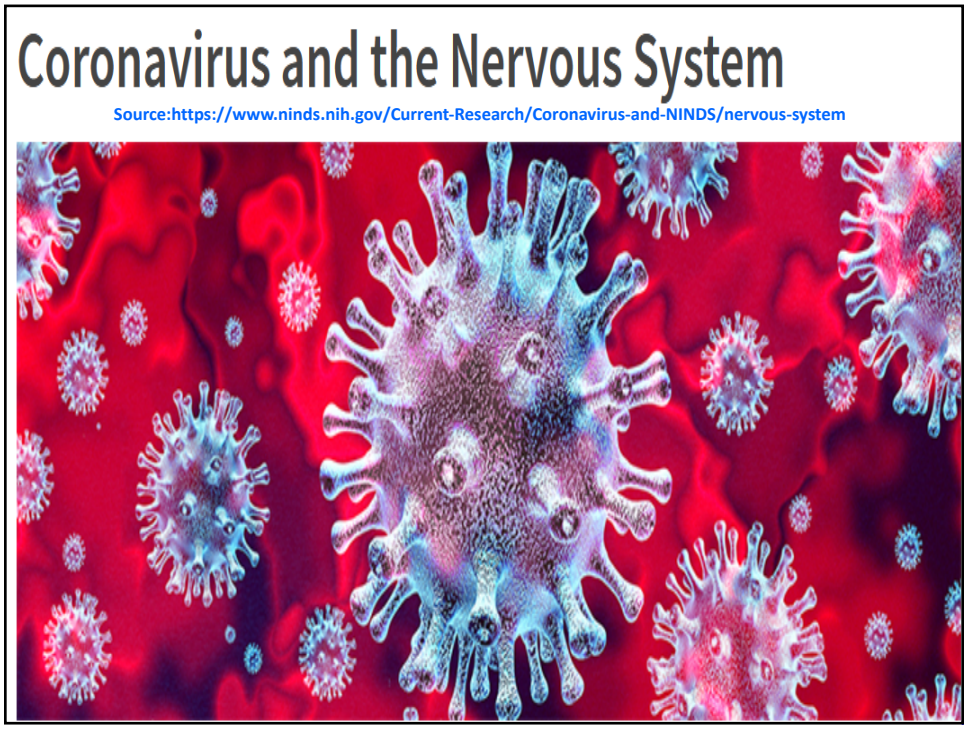
Clinical Syndrome	Potential Pathophysiology
Parainfectious manifestations	
Anosmia	Infection of olfactory epithelium or nerve
Myalgia/rhabdomyolysis	Infection of muscle, medication effects, metabolic derangements
Meningitis/encephalitis	CNS infection
Encephalopathy	Hypoxia, multiorgan failure, medication effects
Seizures	Fever, metabolic derangements, viral encephalitis, stroke
Atypical acute respiratory distress syndrome/Ondine's Curse	Unknown
Post-viral syndromes	
Acute disseminated encephalomyelitis	T cell mediated
Transverse myelitis	Immune cell mediated
Guillain Barre syndrome	Antibody mediated
Acute necrotizing hemorrhagic encephalopathy	Cytokine mediated

Table 1. Source: https://worldneurologyonline.com/article/covid-19-a-neurologists-perspective/

d) Direct Viral Infection of COVID-19 in the Nervous System

- Some reports provide evidence for direct viral invasion of the nervous system.
- In some postmortem case series, SARS-CoV-2 was detected in most brain specimens, but these findings were unrelated to the severity of neuropathological findings. This suggests that neural injury may be due to a systemic inflammatory response triggered by the SARS-CoV-2 virus rather than the infection itself.


SARS CoV-2 Infection
Systemic Disease
CNS Invasion
PNS /muscle involvement
Post-Infectious
MOF
Coagulopathy
Inflammation
Cell death/dysfunction
Cell death/dysfunction
Immune-mediated
Hypoxic/ Metabolic Encephalopathy
Stroke
Inflammatory Encephalopathy Encephalitis* Kawasaki-Like
Viral Encephalitis§ Viral Meningitis§ Viral Endothelialitis §
Anosmia/Ageusia Neuropathy (?) Muscle injury
GBS & Variants ADEM ANE
Source: https://onlinelibrary.wiley.com/doi/full/10.1002/ana.25807


Coronavirus and the Nervous System
Source:https://www.ninds.nih.gov/Current-Research/Coronavirus-and-NINDS/nervous-system

Source: https://onlinelibrary.wiley.com/doi/epdf/10.1002/ana.25807

TABLE. Neurologic Conditions Associated with SARS-CoV-2 Infection

Disease entity	Presentation	Supportive Neurodiagnostic testing	Pathogenesis
Encephalopathy	Altered mental status	MRI: non-specific EEG: abnormal (slow) CSF: nl cells and Pro CSF SARS-CoV-2 RT-PCR: NEG	Multiple organ failure Hypoxemia Systemic Inflammation Endothelialitis
Encephalitis	Altered mental status and CNS dysfunction	MRI: non-specific (? WM changes) EEG: abnormal (slow, +focal) CSF: pleocytosis & elev. Pro CSF SARS-CoV-2 RT-PCR: NEG	CNS inflammation
Viral encephalitis	Altered mental status and CNS dysfunction	MRI: new abnormality EEG: abnormal (slow, ±focal) CSF: Pleocytosis and elev. Pro CSF SARS-CoV-2 RT-PCR: POS Brain Tissue: POS (Ag or RNA)	Brain parenchymal neuro-invasion
Viral meningitis	Headache, nuchal rigidity	MRI: meningeal enhancement, CSF: pleocytosis & elev. Pro CSF SARS-CoV-2 RT PCR: POS	Subarachnoid invasion
Stroke	Focal motor or sensory deficit	MRI: ischemia or bleed, abnormal coagulation factors, increased inflammatory markers	Coagulopathy
Anosmia/ageusia	Olfactory or taste dysfunction	Abnormal smell/taste tests	? Peripheral vs central neuro-invasion
ADEM	Headache, acute neurologic symptoms	MRI: hyperintense FLAIR lesions with variable enhancement	Postinfectious
Guillain-Barre syndrome	Flaccid muscle weakness	CSF: increased protein, nl WBC CSF SARS-CoV-2 RT-PCR: NEG EMG/NCS: abnormal	Postinfectious
Muscle injury	Myalgia	CK elevated	Myopathy or myositis?

ADEM = acute disseminated encephalomyelitis; CNS = central nervous system; CK= creatinine kinase; CSF = cerebrospinal fluid; EEG = electroencephalogram; EMG = electromyogram; FLAIR = fluid-attenuated inversion recovery; MRI = magnetic resonance imaging; NCS = nerve conduction study; NEG = negative; POS = positive; pro = protein; RT-PCR = reverse transcriptase-polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus type 2; WBC = white blood cell; WM = white matter.

What are the immediate (acute) effects of SARS-CoV-2 and COVID-19 on the brain?

- Most people infected with SARS-CoV-2 virus will have no or mild to moderate symptoms associated with the brain or nervous system.
- However, most individuals hospitalized due to the virus do have symptoms related to the brain or nervous system, most commonly including muscle aches, headaches, dizziness, and altered taste and smell.
- Some people with COVID-19 either initially have, or develop in the hospital, a dramatic state of confusion called delirium.
- Although rare, COVID-19 can cause seizures or major strokes.
- Muscular weakness, nerve injury, and pain syndromes are common in people who require intensive care during infections.
- There are also very rare reports of conditions that develop after SARS-CoV-2 infection, as they sometimes do with other types of infections. These disorders of inflammation in the nervous system include Guillain-Barré syndrome (which affects nerves), transverse myelitis (which affects the spinal cord), and acute necrotizing leukoencephalopathy (which affects the brain).Source: https://www.ninds.nih.gov/Current-Research/Coronavirus-and-NINDS/nervous-system#complications

Other Acute Neurologic Manifestations with COVID-19

- Meningoencephalitis
- Rhomboencephalitis
- Acute Disseminated Encephalomyelitis (ADEM) and Acute Hemorrhagic Necrotizing Encephalopathy
- Multisystem Inflammatory Syndrome in Children
- Seizures and Status epilepticus
- Generalized Myoclonus
- Posterior Reversible Encephalopathy Syndrome (PRES)

Fatigue

- The most common persistent symptom weeks and months after COVID-19 infection is fatigue.
- The fatigue is similar to what one experiences with many viral infections such as the flu.
- The sense of fatigue can be brought on by both physical and mental activity. Some people are unable to return to work or school after COVID-19 due to fatigue, while others find it extremely difficult to accomplish their normal level of activity.
- COVID-related complications such as depressed heart, lung, or kidney function, poor sleep, or muscle deconditioning are known to cause fatigue and affect the ability to exercise.
- Fatigue is very common in most inflammatory conditions. The cause(s) of fatigue in many of those suffering weeks and months after COVID-19 is not known.
- Post-exertional malaise (PEM) is a condition in which otherwise usual activities are followed by a period of very severe fatigue and sense of feeling sick.
- PEM can occur with a delay after the activity, but can last for days thereafter.

Source: https://www.ninds.nih.gov/Current-Research/Coronavirus-and-NINDS/nervous-system#complications

Headaches secondary to COVID-19

- Usually occur at the beginning of COVID-19 Infection.
- Usually last 3 to 5 days
- 70% of adults, 60% of children experience headaches
- About 15%, state that their only symptom with COVID-19 was headache

Source: https://www.medicalnewstoday.com/articles/covid-headache#is-it-a-symptom

- Be moderately to severely painful
- Feel 'pulsing', 'pressing' or 'stabbing'
- Occur across both sides of the head (bilateral) rather than in one area
- Last for more than three days
- Be resistant to regular painkillers
- In some patients, the severe headache of COVID-19 only lasts a few days, while in others, it can last up to months. It is presenting mostly as a whole-head, severe-pressure pain. It's different than migraine, which by definition is unilateral throbbing with sensitivity to light or sound, or nausea.

Toward a better understanding of persistent headache after mild COVID-19: Three migraine-like yet distinct scenarios

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Abstract

One year after the outbreak of coronavirus disease 2019 (COVID-19), referrals for persistent headache, often defined as "post-COVID headache," have become increasingly common in outpatient headache clinics. However, it is important to take into consideration that this term may include a spectrum of clinically different headache types. We describe three cases of migraine-like headaches in individuals with a history of mild COVID-19 infection to demonstrate some of the different phenotypes of persistent headaches seen. These cases highlight the importance of a careful evaluation when assessing the complexities of "post-COVID headache" as well as the need to further investigate the different, underlying, pathophysiological mechanisms.

KEYWORDS
headache, migraine, post-COVID-19, SARS-CoV-2

Source:https://headachejournal.onlinelibrary.wiley.com/doi/epdf/10.1111/head.14197

TABLE 1 Main features of the three patients presented

	Patient 1	Patient 2	Patient 3
Demographics			
Age, years	56	55	44
Menopause	Yes	Yes	N/A
Sex	Female	Female	Male
Family migraine history	Yes	No	No
Personal migraine history	Yes	No	No
COVID-19 and headache characteristics			
COVID-19 severity	Mild	Mild	Mild
Headache in the acute phase	Yes	Yes	No
Anosmia/ageusia	Yes	Yes	No
Migraine-like features	Yes	Yes	Yes
Concomitant "post-COVID" symptoms	Fatigue, insomnia	Hyposmia, fatigue, insomnia	Fatigue, insomnia, mood disorder, loss of memory, dizziness
Treatment response			
Response to triptans	Yes	Yes	No
Response to preventive medications (AMT+BTX)	Yes	Yes	No

Abbreviations: AMT, amitryptiline; BTX, onabotulinumtoxinA; N/A, not applicable.

Source: https://headachejournal.onlinelibrary.wiley.com/doi/epdf/10.1111/head.14197

Encephalopathy

Risk factors for encephalopathy include the following:

- Older age
- Vision impairment
- History of Parkinson disease
- History of stroke
- Prior psychoactive medication use

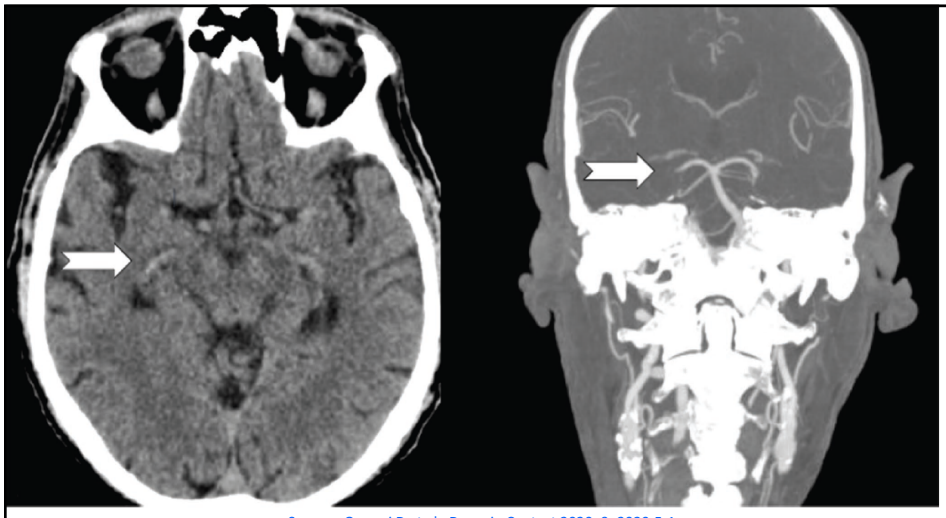
Source: https://www.uptodate.com/contents/covid-19-neurologic-complications-and-management-of-neurologic-conditions

Encephalopathy

Presentation:	Altered mental status
Supportive testing:	MRI: Normal;
	EEG: Abnormal (slowing);
	CSF: Normal;
	CSF: SARS-CoV-2 negative
Treatment:	Supportive; treat underlying COVID-19

CSF = cerebrospinal fluid; EEG = electroencephalogram; MRI = magnetic resonance imaging

Source: https://www.ccjm.org/content/early/2020/08/20/ccjm.87a.ccc058



Source: Orsucci D et al., Drugs in Context 2020; 9: 2020-5-1.

Our patient presented at 70 years with transitory sensory and motor disturbances on the left side of the body (~6 hours). His past medical history was remarkable for hypertension, type 2 diabetes, chronic renal disease, dyslipidemia, and ischemic heart disease with a myocardial infarction. He had an implantable cardioverter-defibrillator and pacemaker (not MRI compatible). He was a smoker. The day before he was discharged from the pneumological unit of our hospital, where he had been hospitalized for 27 days because of COVID-19-related bilateral pneumonia. SARS-Cov-2 RNA was still detectable in his nasopharyngeal specimens by reverse-transcription polymerase chain reaction. Brain CT (left) and angioCT (right) revealed a thrombus in the right cerebral posterior artery (arrows). When he was evaluated, the disturbances were resolved and the neurological examination was normal. Therefore, there were not any criteria for systemic thrombolysis or mechanical thrombectomy, and he was treated with standard medical therapy.

Stroke-Risk Factors

- Most patients are older patients with vascular risk factors.
- Patients with a Hx of CVD, including stroke are at risk of worse outcomes due to COVID-19
- Traditional Risk Factors:
  - HTN
  - Hyperlipidemia
  - Atrial Fibrillation
  - Diabetes mellitus
  - Obesity

Stroke

Presentation:	Acute presentation with focal motor, sensory or speech disturbance
Supportive testing:	MRI: Abnormal, lesion located in a vascular distribution
Treatment:	No society guidelines for COVID-19–specific stroke treatment
	1. Acute ischemic stroke treatment: thrombolytic and endovascular therapy should be considered. No society guidelines on stroke prevention. Therapeutic anticoagulation should be considered on a case-by-case basis.
	2. Acute hemorrhagic stroke (rare): standard treatment with blood pressure control.
	3. Cerebral venous sinus thrombosis: standard treatment with full-dose therapeutic anticoagulation, evaluate for other thrombosis sites.

MRI = magnetic resonance

Source: https://www.ccjm.org/content/early/2020/08/20/ccjm.87a.ccc058

Encephalitis, meningitis

Presentation:	Headache, nuchal rigidity, seizures, focal neurologic deficits; plus altered mental status for encephalitis
Supportive testing:	MRI: Abnormal, WM changes noted; EEG: Abnormal (slow, +/− focal epileptiform discharges);
	CSF: Pleocytosis, elevated protein;
	CSF: SARs-CoV-2, positive
Treatment:	Remains unclear;
	Role for corticosteroids?

CSF = cerebrospinal fluid; EEG = electroencephalogram; MRI = magnetic resonance; WM = white matter

Source: https://www.ccjm.org/content/early/2020/08/20/ccjm.87a.ccc058

Acute disseminated encephalomyelitis

Presentation:	Headache, acute neurologic symptoms
Supportive testing:	MRI: Hyperintense FLAIR lesions with variable enhancement
Treatment:	2 case reports showing improvement with the following:
	• 5 days of IVIG (0.4 g/kg/day)[19]
	• 5 days of IV dexamethasone (20 mg/day) with a 10-day taper[20]

FLAIR = fluid-attenuated inversion recovery; IV = intravenous; IVIG = intravenous immunoglobulin; MRI = magnetic resonance imaging

Source: https://www.ccjm.org/content/early/2020/08/20/ccjm.87a.ccc058

Table 1. Neuromuscular Diseases and COVID-19	
Associated with COVID-19	
Guillain Barre syndrome	Mononeuropathies
Myopathy	Neuromuscular junction disorders
Rhabdomyopathy	Intensive care unit-acquired weakness
Associated with COVID-19 treatments	
Antivirals	Protease inhibitors associated with toxic myopathy and rhabdomyolysis
Antimalarials	Hydroxychloroquine and chloroquine associated with myopathy, neuropathy, myasthenia gravis exacerbation
Azithromycin	Myasthenia gravis exacerbation

Source: https://practicalneurology.com/articles/2021-jan/neuromuscular-medicine-covid-19

Table 2. Considerations for People With Neuromuscular Disease During COVID-19 Pandemic	
Infection and severe disease risks possibly increased by	Tracheostomy
	Noninvasive or invasive ventilation
	Kyphoscoliosis
	Bulbar weakness
	Cardiac involvement
	Metabolic or mitochondrial myopathies increase rhabdomyolysis risk
	Immunosuppressive treatment
	Comorbidities (eg, diabetes, obesity, heart disease)
Exacerbation of neuromuscular disease	Myasthenia gravis flare
Immunotherapy	Increase infection risk both owing to immunosuppression and possible increased exposure of frequent hospital visits for therapies
Social distancing requirements	Reduced access to medications
	Possible delays in diagnosis or treatment
Mitigation strategies	
90-day prescriptions and home delivery of medication	
Consider exposure risk vs interruption of therapy	
Consider reducing dose or frequency of dosing if disease stable	
Switch to home infusions or subcutaneous immunoglobulin (Ig)	

Source: https://practicalneurology.com/articles/2021-jan/neuromuscular-medicine-covid-19

NEUROMUSCULAR DISORDERS

Presentation

Myalgias

Supportive testing

Creatine kinase elevated

Muscle biopsy shows necrosis

Treatment

Supportive; remains unclear

Role for corticosteroids?

Physical therapy

Source: https://www.ccjm.org/content/87/12/729

Acute inflammatory demyelinating polyneuropathy[a]

Presentation:	Flaccid paralysis +/ − respiratory compromise, cranial nerve deficits
Supportive testing:	CSF: Increased protein, normal WBC;
	NCS: Abnormal, axonal and demyelinating variants noted
Treatment:	Standard GBS treatment with 5 days of IVIG (0.4 g/kg/day)
	Case series noted only minimal improvement in 2 of 5 patients post-treatment[28]

CSF = cerebrospinal fluid; GBS = Guillain-Barre syndrome; IVIG = intravenous immunoglobulin; NCS = nerve conduction study; WBC = white blood cells

[a] Also known as Guillain-Barre syndrome.

Source: https://www.ccjm.org/content/early/2020/08/20/ccjm.87a.ccc058

September 15, 2021 | 2 min read SAVE

COVID-19 vaccine exhibits minimal risk for recurrent Guillain-Barré syndrome

Source: https://www.healio.com/news/neurology/20210915/covid19-vaccine-exhibits-minimal-risk-for-recurrent-guillainbarr-syndrome?utm_source=selligent&utm_medium=email&utm_campaign=news&M_BT=1969458496999

ADD TOPIC TO EMAIL ALERTS

The mRNA COVID-19 vaccine was safe in patients previously diagnosed with Guillain-Barré syndrome, with only one patient needing medical care for a short period, according to a study published in *JAMA Neurology*.

"On Dec. 20, 2020, Israel initiated a national vaccination program against COVID-19," **Shirley Shapiro Ben David, MD,** from Health Division, Maccabi Healthcare Services, Tel Aviv, Israel, and colleagues wrote. "National and international vaccine guidelines did not preclude patients who have previously been diagnosed with Guillain-Barré syndrome (GBS) from receiving the COVID-19 vaccine.

JAMA | Original Investigation

Association of Receipt of the Ad26.COV2.S COVID-19 Vaccine With Presumptive Guillain-Barré Syndrome, February-July 2021

Emily Jane Woo, MD, MPH; Adamma Mba-Jonas, MD, MPH; Rositsa B. Dimova, PhD; Meghna Alimchandani, MD; Craig E. Zinderman, MD, MPH; Narayan Nair, MD

IMPORTANCE As part of postauthorization safety surveillance, the US Food and Drug Administration (FDA) has identified a potential safety concern for Guillain-Barré syndrome (GBS) following receipt of the Ad26.COV2.S (Janssen/Johnson & Johnson) COVID-19 vaccine.

OBJECTIVE To assess reports of GBS received in the Vaccine Adverse Event Reporting System (VAERS) following Ad26.COV2.S vaccination.

DESIGN, SETTING, AND PARTICIPANTS Reports of presumptive GBS were identified in a US passive reporting system (VAERS) February-July 2021 and characterized, including demographics, clinical characteristics, and relevant medical history.

EXPOSURES Receipt of the Ad26.COV2.S vaccine; the comparator was the background rate of GBS in the general (unvaccinated) population that had been estimated and published based on a standardized case definition.

MAIN OUTCOMES AND MEASURES Presumptive GBS; the reporting rate was analyzed, including calculation of the observed to expected ratio based on background rates and vaccine administration data. Because of limited availability of medical records, cases were not assessed according to the Brighton Collaboration criteria for GBS.

RESULTS As of July 24, 2021, 130 reports of presumptive GBS were identified in VAERS following Ad26.COV2.S vaccination (median age, 56 years; IQR, 45-62 years; 111 individuals [86.0%] were < 65 years; 77 men [59.7%]). The median time to onset of GBS following vaccination was 13 days (IQR, 10-18 days), with 105 cases (81.4%) beginning within 21 days and 123 (95.3%) within 42 days. One hundred twenty-one reports (93.1%) were serious, including 1 death. With approximately 13 209 858 doses of vaccine administered to adults in the US, the estimated crude reporting rate was 1 case of GBS per 100 000 doses administered. The overall estimated observed to expected rate ratio was 4.18 (95% CI, 3.47-4.98) for the 42-day window, and in the worst-case scenario analysis for adults 18 years or older, corresponded to an estimated absolute rate increase of 6.36 per 100 000 person-years (based on a rate of approximately 8.36 cases per 100 000 person years [123 cases per 1 472 162 person years] compared with a background rate of approximately 2 cases per 100 000 person years). For both risk windows, the observed to expected rate ratio was elevated in all age groups except individuals aged 18 through 29 years.

CONCLUSIONS AND RELEVANCE These findings suggest a potential small but statistically significant safety concern for Guillain-Barré syndrome following receipt of the Ad26.COV2.S vaccine. However, the findings are subject to the limitations of passive reporting systems and presumptive case definition, and they must be considered preliminary pending analysis of medical records to establish a definitive diagnosis.

Author Affiliatio
Biostatistics and

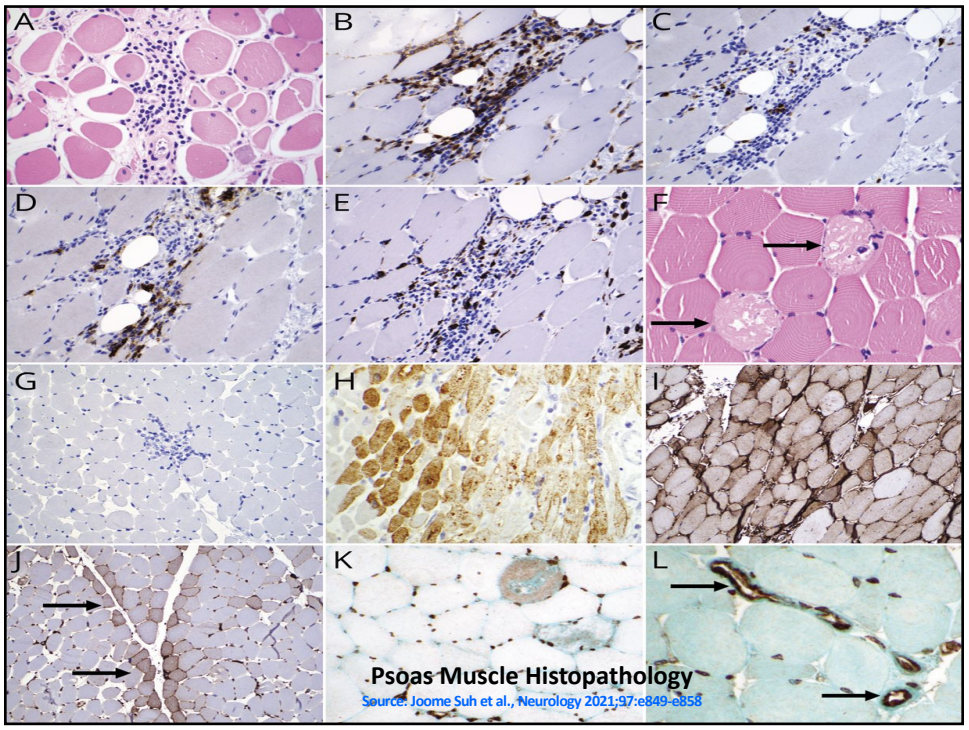
Nerve Damage including Peripheral Neuropathy In COVID-19

- Motor
- Sensory
- Autonomic

Focal and Multifocal Neuropathies secondary to COVID-19 infection

- Facial Nerve Palsy
- Ocular Motor Neuropathies
- Lower Cranial Neuropathy (vagus, accessory, and hypoglossal; Tapia syndrome-synchronous paresis/paralysis of the Vagus and Hypoglossal nerves)
- Multiple Cranial Neuropathies
- Neuralgic Amyotrophy

Source: https://www.uptodate.com/contents/covid-19-neurologic-complications-and-management-of-neurologic-conditions?search=covid-19-neurologic-complications&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1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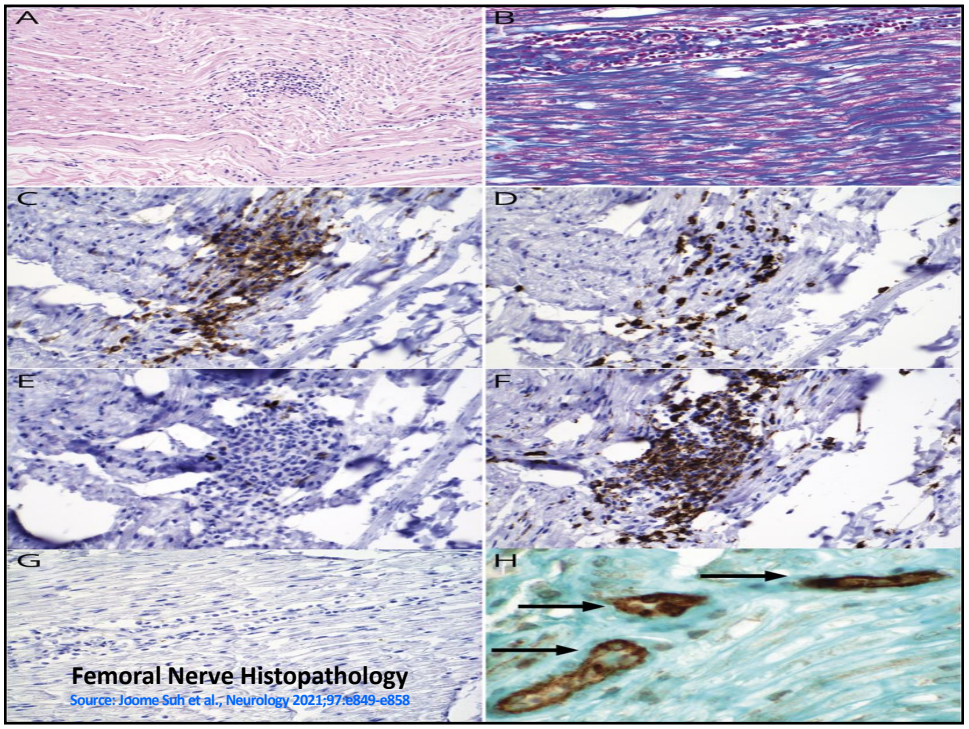
Psoas Muscle Histopathology
Source: Joome Suh et al., Neurology 2021;97:e849-e858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Femoral Nerve Histopathology
Source: Joome Suh et al., Neurology 2021;97:e849-e858

Anosmia/dysgeusia

Presentation:	Olfactory or taste dysfunction
Supportive testing:	Abnormal smell and taste evaluation
Treatment:	Supportive: Improvement noted by 2 weeks post-symptom onset

Source: https://www.ccjm.org/content/early/2020/08/20/ccjm.87a.ccc058

Prolonged/lingering loss of smell (anosmia) or taste

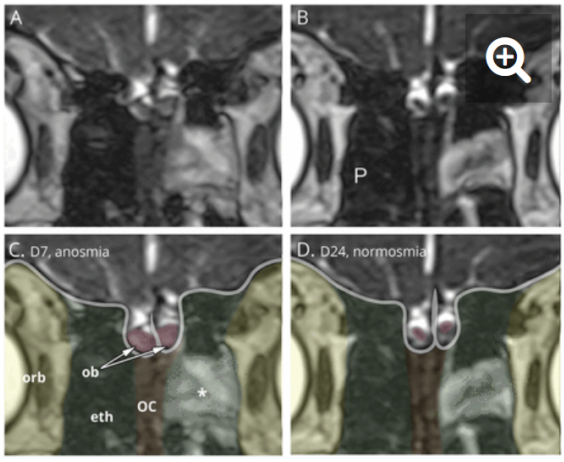
- Some people who have had COVID-19 may lose or experience a perturbation of their sense of taste or smell, or the sensation of flavor.
- The loss of sense of taste or smell is characteristic of COVID-19 because the SARS-CoV-2 virus infects the tissue that forms the lining in the nose.
- The virus has been found to target certain cells in the nose that support the nerve cells. Those nerve cells detect odors and send that information to the brain. Damage to these supporting cells can cause smell or taste loss that can continue for weeks or months as these cells repair themselves or are replaced by new cells.
- During the recovery period some odors may smell different—even sometimes unpleasant or foul—than people remember prior to being infected.

Source: https://www.ninds.nih.gov/Current-Research/Coronavirus-and-NINDS/nervous-system#complications

Smell/Taste Dysfunction

- Smell and taste loss is highly prevalent in COVID-19 of all levels of severity.
- Most patients recover fast, but one out of ten have not recovered in two months.
- The recovery rates up to two months do not correlate with the COVID-19 and chemosensory loss severity.
- The time from chemosensory loss to recovery for the patients who recover is associated with the severity of impairment.
- Less severe hyposmia tends to resolve quicker.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7957474/



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Source: Thomas Laurendon et al. Neurology 2020;95:224-225

Figure

Transient olfactory bulb edema

Coronal 3D constructive interference in steady-state T2-weighted imaging (1.5T) during anosmia (day 7; A, C) compared to recovery (day 24; B, D). MRI shows olfactory bulb (ob; pink) transient volume and signal increase, olfactory cleft edema (OC; brown), and focal left ethmoid (eth; green) sinusitis (*), and normal cranial fossa (gray line) and orbit (orb; yellow).

NEUROCOGNITIVE IMPAIRMENT

Presentation

Neurocognitive impairments in at least 1 domain after COVID-19

Supportive testing

Formal neurocognitive assessment

Treatment

Consideration for neurorehabilitation programs

Source: https://www.ccjm.org/content/87/12/729

Cognitive Impairment/Altered Mental Status

- People with severe acute COVID-19 illness may develop confusion, delirium, and a depressed level of consciousness.
- Those suffering from post-acute sequelae of COVID-19 frequently have difficulty concentrating and memory problems, sometimes called “brain fog.” This impairment is a common symptom in those with severe fatigue of any cause.
- A variety of immune, metabolic, or blood vessel abnormalities or drug effects can contribute to the dramatic effects on cognitive function in the acute infection. Whether these also underlie the problems experienced weeks or months after mild or moderate illness is not known.

Source: https://www.ninds.nih.gov/Current-Research/Coronavirus-and-NINDS/nervous-system#complications

Nakamura et al. BMC Infect Dis (2021) 21:993
https://doi.org/10.1186/s12879-021-06683-7

BMC Infectious Diseases

CASE REPORT Open Access

Case report of restless anal syndrome as restless legs syndrome variant after COVID-19

Itaru Nakamura[1,2*], Takao Itoi[1] and Takeshi Inoue[1]

Abstract

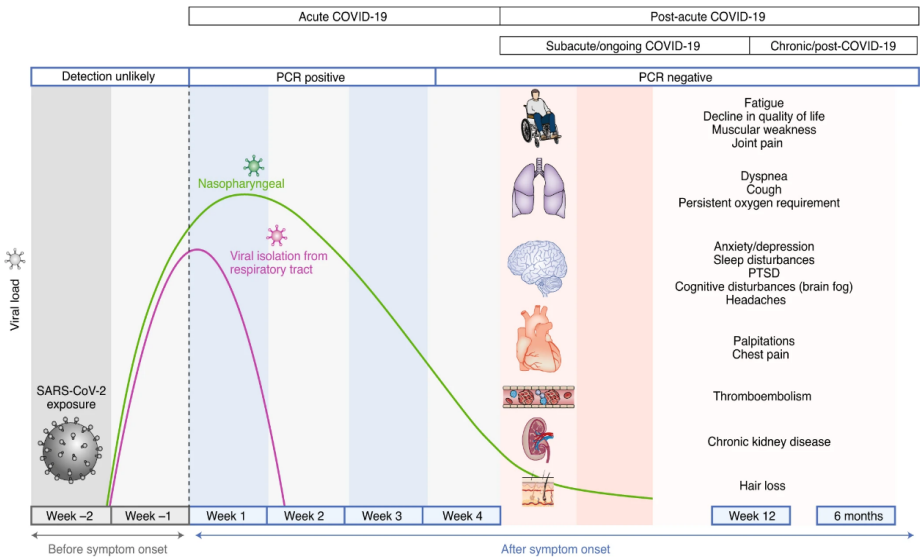
Background: Coronavirus disease 2019 (COVID-19) has a broad spectrum from respiratory and nasopharyngeal symptoms, cerebrovascular diseases, impaired consciousness, and skeletal muscle injury. Emerging evidence has indicated the neural spread of this novel coronavirus. Restless legs syndrome (RLS) is a common neurological, sensorimotor disorder, but highly under diagnosis disorder. Restless anal syndrome as restless legs syndrome variant associated with COVID-19 has been previously not published. We report a case presenting with restless anal syndrome following COVID-19.

Case presentation: Although a 77-year-old male with COVID-19 improved to normal respiratory function 21 days after admission and treatment of favipiravir 200 mg per day for 14 days and dexamethasone 6.6 mg per day for 5 days, the insomnia and anxiety symptoms remained. Several weeks after discharge, he gradually began to experience restless, deep anal discomfort, approximately 10 cm from the perineal region. The following features were observed in the anal region; urge to move is essential, with worsening with rest, improvement with exercise, and worsening at evening. Colonoscopy revealed internal haemorrhoids without other rectal lesions. Neurological findings including deep tendon reflex, perineum loss of sensory and spinal cord injury, revealed no abnormalities. Diabetes militias, kidney dysfunction and iron deficiency status were not confirmed. Family history of RLS and periodic limb movements were not observed. Clonazepam at 1.5 mg per day resulted in the alleviation restless anal discomfort.

Conclusions: We reported a case presenting with restless anal syndrome following affection of COVID-19 as restless legs syndrome variant. This case fulfilled 4 essential features of RLS, urge to move, worsening with rest, improvement with exercise, and worsening at evening. To date, no case of restless anal syndrome associated with COVID-19 has been previously published. This case report may reflect the associative impacts of COVID-19 on the neuropsychiatric state. The long-term outcomes of neuropsychiatric conditions should continue to be monitored.

Keywords: COVID-19, Anal, Restless, Complication, Neuropsychiatric

From: Post-acute COVID-19 syndrome



Acute COVID-19 usually lasts until 4 weeks from the onset of symptoms, beyond which replication-competent SARS-CoV-2 has not been isolated. Post-acute COVID-19 is defined as persistent symptoms and/or delayed or long-term complications beyond 4 weeks from the onset of symptoms. The common symptoms observed in post-acute COVID-19 are summarized.

Source: https://www.nature.com/articles/s41591-021-01283-z/figures/1

Long-Haul COVID-19

Also known as the following:

- Long COVID
- Long-haul COVID
- Long-term COVID
- Post-COVID Syndrome
- Post-acute Sequelae of SARS-COV-2 Infection
- Post-COVID Conditions

What are possible long-term neurological complications of COVID-19?

Researchers are following some known acute effects of the virus to determine their relationship to the post-acute complications of COVID-19 infection. These post-acute effects usually include fatigue in combination with a series of other symptoms. These may include trouble with concentration and memory, sleep disorders, fluctuating heart rate and alternating sense of feeling hot or cold, cough, shortness of breath, problems with sleep, inability to exercise to previous normal levels, feeling sick for a day or two after exercising (post-exertional malaise), and pain in muscle, joints, and chest.#1

Headache is also a long-haul COVID symptom in some patients.#2

Source#1: https://www.ninds.nih.gov/Current-Research/Coronavirus-and-NINDS/nervous-system#complications
Source#2: Source: Sampaio Rocha- Filho PA, Voss L. Persistent headache and persistent anosmia associated with COVID- 19. Headache. 2020;60(8):1797- 1799.

A prospective study of long-term outcomes among hospitalized COVID-19 patients with and without neurological complications

Results:

- Of 606 COVID-19 patients with neurological complications, 395 survived hospitalization and were matched to 395 controls; *N* = 196 neurological patients and *N* = 186 controls completed follow-up.
- Overall, 346/382 (91%) patients had at least one abnormal outcome: 56% had limited ADLs (walking, feeding, dressing/grooming, toileting, bathing, transferring), 50% impaired cognition, 47% could not return to work and 62% scored worse than average on ≥1 Neuro-QoL scale (worse anxiety 46%, sleep 38%, fatigue 36%, and depression 25%).
- In multivariable analysis, patients with neurological complications had worse 6-month mRS (median 4 vs. 3 among controls, adjusted OR 1.98, 95%CI 1.23–3.48, *P* = 0.02), worse ADLs (aOR 0.38, 95%CI 0.29–0.74, *P* = 0.01) and were less likely to return to work than controls (41% versus 64%, *P* = 0.04). Cognitive and Neuro-QOL metrics were similar between groups.

Source: https://www.jns-journal.com/article/S0022-510X(21)00180-5/fulltext

A prospective study of long-term outcomes among hospitalized COVID-19 patients with and without neurological complications

- Abnormalities in functional outcomes, ADLs, anxiety, depression and sleep occurred in over 90% of patients 6-months after hospitalization for COVID-19.
- In multivariable analysis, patients with neurological complications during index hospitalization had significantly worse 6-month functional outcomes than those without. Source: https://www.jns-journal.com/article/S0022-510X(21)00180-5/fulltext

Sleep Disturbances

- Some people with long-term neurological effects from the SARS-CoV-2 infection report having trouble falling asleep or staying asleep (insomnia), excessive daytime sleepiness (hypersomnia), unrefreshing sleep, and changes in sleep patterns. It may be difficult for some people to wake up and fall asleep at their regular times. Depression, anxiety, and post-traumatic stress disorder (PTSD) can negatively affect sleep. Sleep disorders can contribute to fatigue and cognitive troubles. Some people report an increase in pain, headache, and stress because of lack of sleep. Continued loss of sleep also negatively affects attention and mood.

Source: https://www.ninds.nih.gov/Current-Research/Coronavirus-and-NINDS/nervous-system#complications

Does the COVID-19 Vaccine cause Neurological Problems?

- Almost everyone should get the COVID-19 vaccination. It will help protect you from getting COVID-19. The vaccines are safe and effective and cannot give you the disease. Most side effects of the vaccine may feel like flu and are temporary and go away within a day or two. In early vaccine development, there were extremely rare reports of unexplained neurological illness following COVID-19 vaccination, but regulators found no evidence the vaccines caused the illness. The U.S. Food and Drug Administration (FDA) continues to investigate any report of adverse consequences of the vaccine and none have appeared as of yet. Consult your primary care doctor or specialist if you have concerns regarding any pre-existing known allergic or other severe reactions and vaccine safety. Scientists are studying the risk to benefit ratio of the vaccine in someone who previously developed Guillain Barré syndrome after a vaccination. The general sense is the COVID-19 vaccine is safe in individuals whose Guillain-Barré syndrome was not associated with a previous vaccination.
- The U.S. Centers for Disease Control and Prevention (CDC) site offers information on vaccine resources. The National Institutes of Health (NIH) has information on vaccines for the coronavirus.

Prevention for COVID-19

- Wash your hands
- Wear facial masks
- Social Distancing
- Mitigate risk factors
- Utilization of Telemedicine where applicable
- Vaccinations
  - mRNAs (Pfizer and Moderna)
  - Johnson & Johnson vaccine

Key Points

- Human coronaviruses, including SARS-CoV-2 can affect the nervous system.
- Neurologic complications include encephalopathy, neuromuscular disorders, and acute cerebrovascular disorders.
- Postinfectious demyelination, encephalitis and Sz are likely underreported.
- Long-term neurological sequelae do occur.

Source: https://www.ccjm.org/content/87/12/729

Figure

Atlas Covidicus, acrylic painting by Jamie Newman, 2020.

Source:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7428451/

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