
In The Name of God

Neurologic manifestation of covid 19 (PNS)

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As knowledge of SARS-CoV-2 and its clinical appearance continue to grow, the literature has shown a significant number of infected patients exhibit neurological symptoms(50 percent of hospitalized patients).

we discussed various neurological manifestations reported in COVID19 patients and hypothesize their underlying pathophysiology as knowledge of SARS-CoVID.

COVID-19 and Major Reported Neurological Abnormalities

Central Nervous System (Mostly inflammation-mediated)

- Headache
- AMS
- Delirium
- CVA (both ischemic and hemorrhagic)
- Seizures
- Infectious Toxic Encephalopathy
- Acute Encephalitis
- Meningitis
- Dysexecutive Syndrome

Peripheral Nervous System (Mostly immune-mediated)

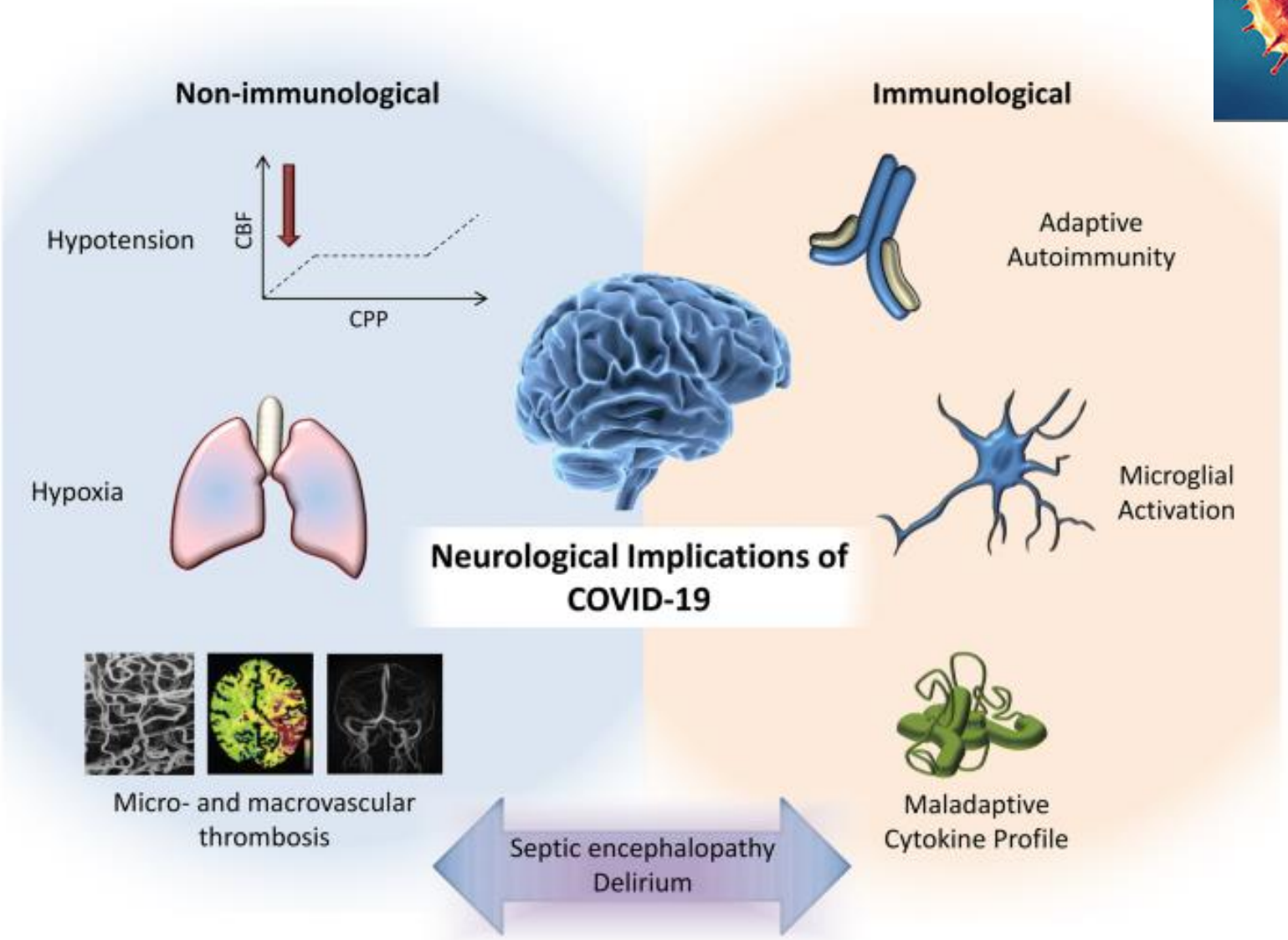
- Dysosmia/anosmia
- Dysgeusia/ageusia
- Acute Myelitis
- GBS
- Miller Fisher Syndrome
- Polyneuritis Cranialis

Musculoskeletal (Direct injury)

- Atonia
- Paresis

Peripheral Nervous System Manifestations of COVID-1

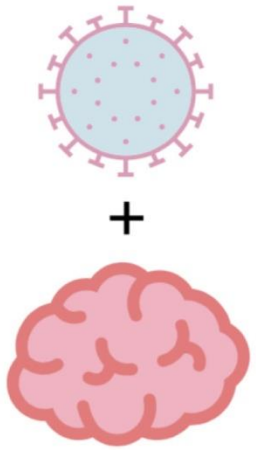
- Nerve pain and skeletal muscle injury
- Guillain-Barré syndrome
- Cranial polyneuritis
- Neuromuscular junction disorders
- Neuro-ophthalmological disorders
- Neurosensory hearing loss
- Dysautonomia


Non-immunological
Immunological
Hypotension
CBF
CPP
Adaptive
Autoimmunity
Hypoxia
Microglial
Activation
Neurological Implications of
COVID-19
Micro- and macrovascular
thrombosis
Maladaptive
Cytokine Profile
Septic encephalopathy
Delirium

COVID-19 Neurologic Complications

Pathophysiology

- Direct damage to receptors
- Cytokine-related injury
- Secondary to hypoxia
- Retrograde travel along nerve fibers



Major complications

- Acute cerebrovascular disease
- Encephalitis and encephalopathy
- Guillain-Barré Syndrome
- Hemophagocytic Lymphohistiocytosis
- Medication interactions

Pathophysiology of CNS involvement of COVID 19

Corona virus can affect CNS by several mechanisms based on routes of entry.

Most notable entrance way : intranasal inoculation and peripheral nerves using retrograde trans-synaptic pathways.(direct invasion)

Coronaviruses can infect both neurone and neuroglia cells which both express the entry protein ACE2 and associate with necrosis and apoptosis of neuronal cells and stimulate T cell-mediated autoimmune reactions against CNS antigens. ACE2 receptor binding affinity to new corona virus spike proteins is approximately 15 fold higher than the SARS-covid spike

Another route of entry is direct invasion of coronavirus to brain tissue by invading endothelial of micro-capillaries in brain production of viral toxins and inflammatory mediators.

Cytokine storm that started with interleukin-6 and provoke release of TNF-α, G-CSF, MCP-1, IP-10, IL-8, IL-10 and MIP-1A which result in activation of glutamate receptors, hyper-excitability of neurons and play a key roll in seizure developing. Moreover, inflammatory processes and immunologic responses may cause in injury and edema, leading to changes in consciousness status

Transmission

Netland, J et al. revealed that virus existence in microcirculation in brain can invade CNS indirectly by brain capillary endothelium invasion through interaction between virus spike protein and ACE2 receptor of capillary. Therefore, endothelium damage let virus access to brain and interact with ACE2 receptor of neuronal tissue. This could be fetal due to capillary bleeding in brain tissue.

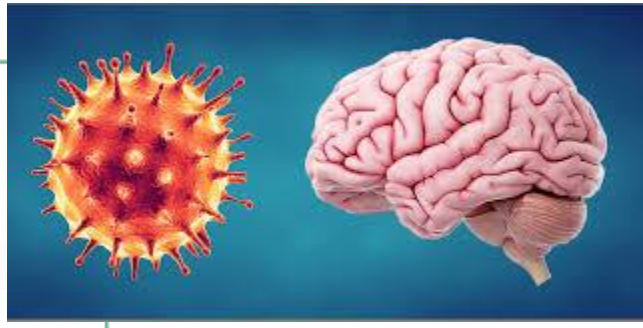
The most probable way for SARS- covid virus is by endings of peripheral nerves and synaptic connections (specialty olfactory nerve).

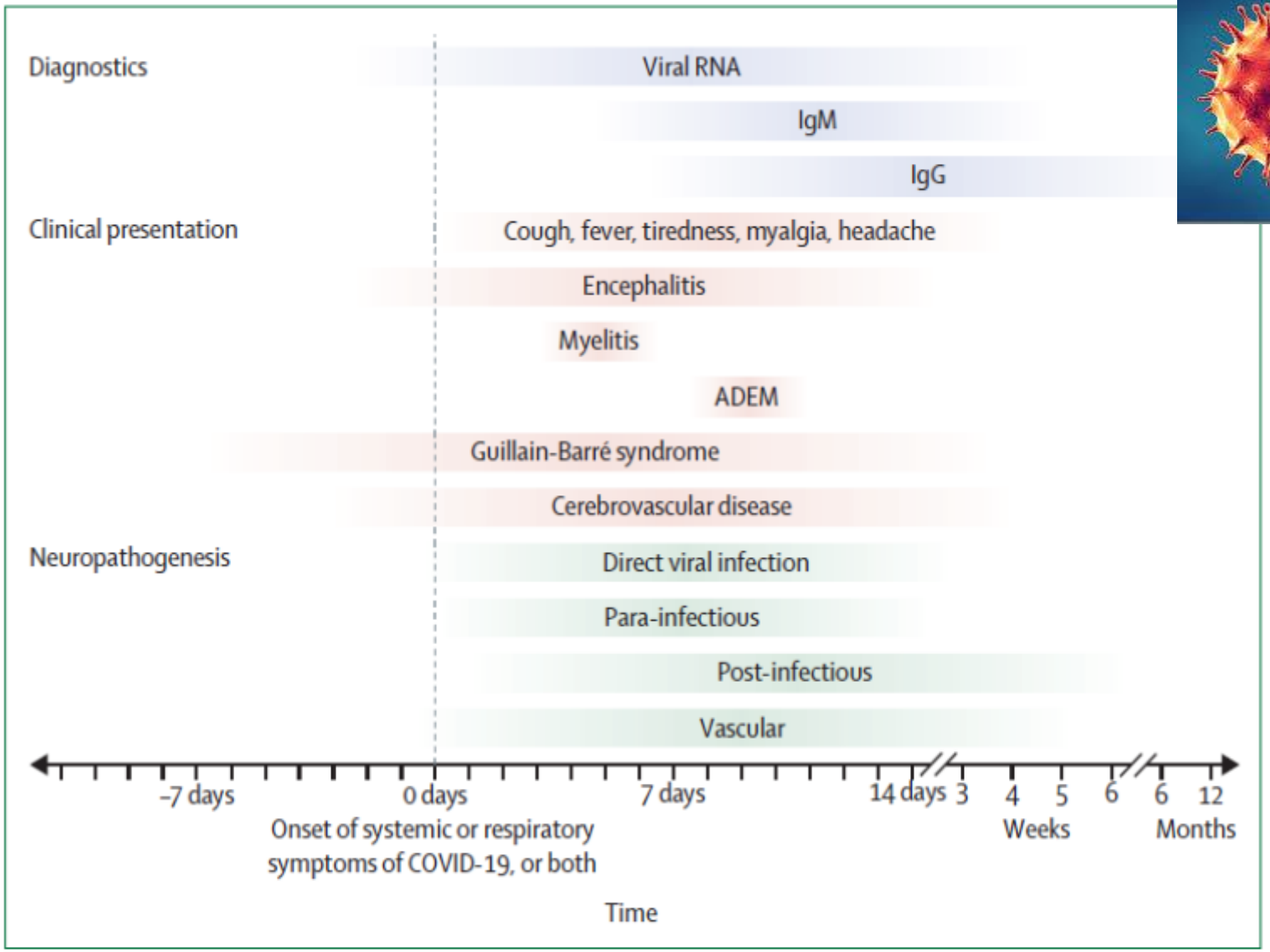
Some article revealed cases which showed virus existence in brain tissue but not in lung or other parts of respiratory tract.

Moreover, virus antigen was detected in olfactory nerve and other CNS regions are interconnected with the olfactory bulb including piriform and infralimbic cortices, basal ganglia and midbrain after 60 hours' post-infection.

However, high viral load in brain stem in sever corona virus infected patients with respiratory manifestations defenestrate the spreading of virus to CNS through Vagus nerves to the ambigus and solitary tract nuclei.

Approximate timeline for positive diagnostic tests, clinical presentation, and pathogenesis in COVID-19-associated neurological disease





Guillain barre syndrome

- Incidence is not particularly higher than what might be expected.(Italy hospital :1200 patients -5 had GBS)
- A recent epidemiological study in the UK does not confirm a causal link of COVID-19 to GBS
- The annual incidence of GBS in UK hospitals was 1.66 to 1.88 per 100,000 people for the years 2016 to 2019
- Significantly fewer GBS cases were reported for March, April, and May 2020 (93, 70, and 56, respectively) compared with 2016–2019 mean case numbers for the same months (132,116, and 113, respectively)
- Neurological symptoms started at a median of 7 days (range –7 to 24) after respiratory or systemic features , although two patients developed febrile illness 7 days after the onset of Guillain-Barré syndrome
- Two patients with miller fisher variant of GBS
- All type is seen (demyelinating ,AMAN ,AMSAN ,miller fisher)
- Post covid vaccine also seen

Cranial nerve palsy

- All nerve involvement was seen
- Most common : 1,7,6,3
- Loss of smell (anosmia) and taste (ageusia) have emerged as common symptoms of COVID-19
- (50% of hospitalized patients with covid)
- In a European study, olfactory dysfunction was reported for 357 (86%) of 417 COVID-19 patients; 342 (82%) reported gustatory disorders.

Nerve pain ,myalgia ,muscle injury

- Nerve pain was found in patients with severe and non-severe COVID-19,
- Skeletal muscle injury was seen in patients with severe and non-severe COVID-19
- Creatine kinase (CK) elevation, as the only marker of muscle injury, are non-specific and may be related to prolonged bed rest and medications in severe COVID-19 cases more than a direct muscle injury from COVID-
- Muscle : myalgia 14.9% ---higher CPK 12.5% in non sever cases ,19% in sever cases --0.2 % rhabdomyolysis
- “Intensive care unit-acquired weakness (ICUAW) critical illness myopathy (CIM), critical illness neuropathy (CIN)

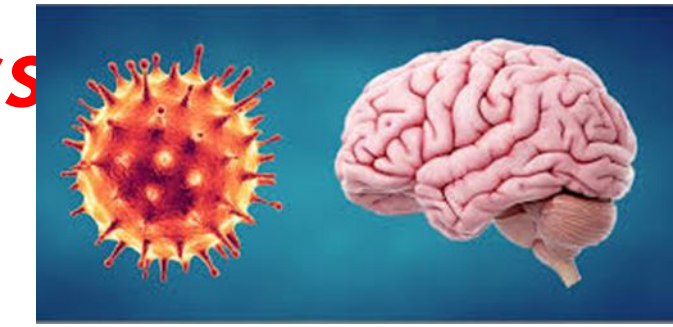
Complication of prone position

- However, several neurological issues may arise from prone positioning
- Rise in intracranial pressure
- Brachial plexus damage , and radial, median, and sciatic nerve injury
- The most common site of injury was the ulnar nerve (28.6%), followed by the radial nerve (14.3%), the sciatic nerve (14.3%), the brachial plexus (9.5%), and the
- median nerve (9.5%).

Rare PNS complication of covid

- Opsoclonus after covid 19 : infant 4 month with opsoclonus one month after covid
-
- Nystagmus post covid
-
- Transient acetylcholin receptor related myasthenia gravis post (MIS-C)
- A 7 years old girl present with fatigable bilateral ptosis ,diplopia,positive ocular cold compression test

COVID-19 during pregnancy and the poss mental complications in neonates



- The COVID-19 is profoundly affecting mental health in infected individuals and increasing the risk of psychological problems in non-infected individuals, especially in pregnant women and children
- Anxiety, anger, fear, and disturbed wake and sleep routines that may alter the hormonal balance by affecting the **hypothalamic-pituitary-gonadal axis**
- These problems may cause adverse pregnancy and neonatal outcomes, such as the increased risk of schizophrenia in neonates
- Maternal psychosocial stress can adversely affect the development and maturation of the fetal brain in response to elevated **maternal cortisol and cytokines** levels and disrupted serotonin homeostasis
- Affect the vaginal ecosystem and microbiome, which induces disruption of the fetal gut-brain axis, thereby developing neurodevelopmental disorders in growing children
- Maternal psychosocial stress can also increase susceptibility to several medical conditions such as :
- smaller head circumference, low birth weight, preterm birth, morphological, and physiological alteration in the fetal brain, and neurobehavioral disorders (schizophrenia, autism, learning disorders, and mood disorders)

Long term out come of covid in children

- We know that normal daily routines and mental health inevitable to maintain proper circadian rhythms
- In the current scenario of the COVID-19 pandemic, individuals are restricted from outdoor activities, which affect their daily schedules, such as sleep-wake timing and eating routines
- Thus, the chances of rhythm disruption are increased. Exposure to light at night and disturbed sleep patterns in children induces perturbation of the circadian rhythm, leading to **mood disorders, anxiety, and sleep disorders**
- Moreover, limited exposure to the outdoor environment and higher access to **electronic devices** may increase children's risk of severe mental illnesses

Neurological Signs and Symptoms in Multi-System Inflammatory Syndrome

Headache, altered mental status, and aseptic meningitis Headache was the most common symptom , affecting 26% of patients

- In a larger survey of 186 children, 5–11% had neurologic involvement, depending on age, including encephalitis, seizures , weakness, ataxia, and dysarthria
- Brain MRI scans showed abnormal signal intensities of the splenium of the corpus callosum ,demyelinating lesion

Complication of covid vaccine

- Overall, the local reactions to vaccination were mild; however, moderate-to-severe systemic side effects, such as
- fatigue, myalgia, arthralgia, and headache, were noted in about 50% of participants in the mRNA-1273 group after the second dose
- These side effects were transient, starting about 15 h after vaccination and resolved in most participants by day 2, without sequelae
- Bells palsy was extremely rare 3days to 48 days post vaccine
- in the Pfizer-BioNTech clinical trial, which included 44,000 participants, 4 people reported experiencing Bell's palsy, a total of 0.0091% of participants
- In the Moderna trial, which included 30,400 participants, 3 people (0.099%)
- Guillain barre syndrome
- Transverse myelitis

Neurological Events Reported after COVID-19 Vaccines: An Analysis of Vaccine Adverse Event Reporting System

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Objective: To identify the rates of neurological events following administration of mRNA (Pfizer, Moderna) or adenovirus vector (Janssen) vaccines in the U.S.

Methods: We used publicly available data from the U.S. Vaccine Adverse Event Reporting System (VAERS) collected between January 1, 2021 and June 14, 2021. All free text symptoms that were reported within 42 days of vaccine administration were manually reviewed and grouped into 36 individual neurological diagnostic categories. Post-vaccination neurological event rates were compared between vaccine types and to age-matched baseline incidence rates in the U.S. and rates of neurological events following COVID.

Results: Of 306,907,697 COVID vaccine doses administered during the study timeframe, 314,610 (0.1%) people reported any adverse event and 105,214 (0.03%) reported neurological adverse events in a median of 1 day (IQR0-3) from inoculation. Guillain-Barre Syndrome (GBS), and cerebral venous thrombosis (CVT) occurred in fewer than 1 per 1,000,000 doses. Significantly more neurological adverse events were reported following Janssen (Ad26.COV2.S) vaccination compared to either Pfizer-BioNtech (BNT162b2) or Moderna (mRNA-1,273; 0.15% vs 0.03% vs 0.03% of doses, respectively, $p < 0.0001$). The observed-to-expected ratios for GBS, CVT and seizure following Janssen vaccination were ≥1.5-fold higher than background rates. However, the rate of neurological events after acute SARS-CoV-2 infection was up to 617-fold higher than after COVID vaccination.

Interpretation: Reports of serious neurological events following COVID vaccination are rare. GBS, CVT and seizure may occur at higher than background rates following Janssen vaccination. Despite this, rates of neurological complications following acute SARS-CoV-2 infection are up to 617-fold higher than after COVID vaccination.

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Thank you for Attention
Meredith Carlson Photography