



NEUROLOGICAL COMPLICATIONS OF COVID-19

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November 2021

DISCLOSURES

- Dr. Bernard has no disclosures relevant to this topic

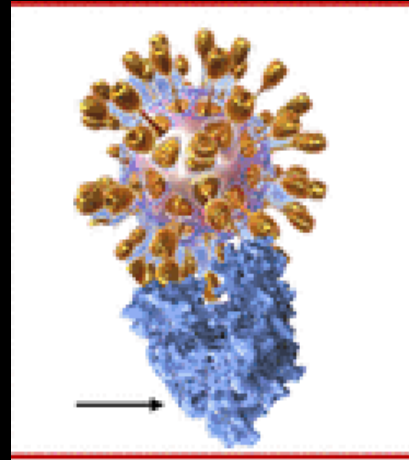
NEUROLOGICAL COMPLICATIONS OF COVID-19

- Review pathophysiology of Covid-19 infection and acute neurological complications
- Review impact of treatment of Covid-19 on the CNS, specifically ECMO
- Review complications of Covid-19 in previously diagnosed and undiagnosed neurological conditions
- Review neurological complications of vaccinations for COVID-19 and discuss implications for neurological diseases
- Review Long –Covid syndrome, or “Post Acute Sequelae SARS- C oV-2 infection (PASC)” ; risk factors, symptoms, approaches

WHAT IS SARS-COV-2?

- It has now been shown that the virus causing COVID-19 is a SARS-like coronavirus that had previously been reported in bats in China.
- SARS-CoV-2 is a human coronavirus: an enveloped, single-stranded ssRNA virus characterized by its crown-like morphology with a genome comprised of 29,903 bp
- The coronavirus disease of 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
- With the mRNA encoding several other proteins, the COVID-19 virus uses a spike protein S1 that enables the attachment of the virion to the cell membrane by interacting with host ACE2 receptor

COVID-19 DOCKS ON THE ACE2 RECEPTOR
VIA SPIKE PROTEIN, ENTERS THE CELL AND
BEGINS TO REPLICATE

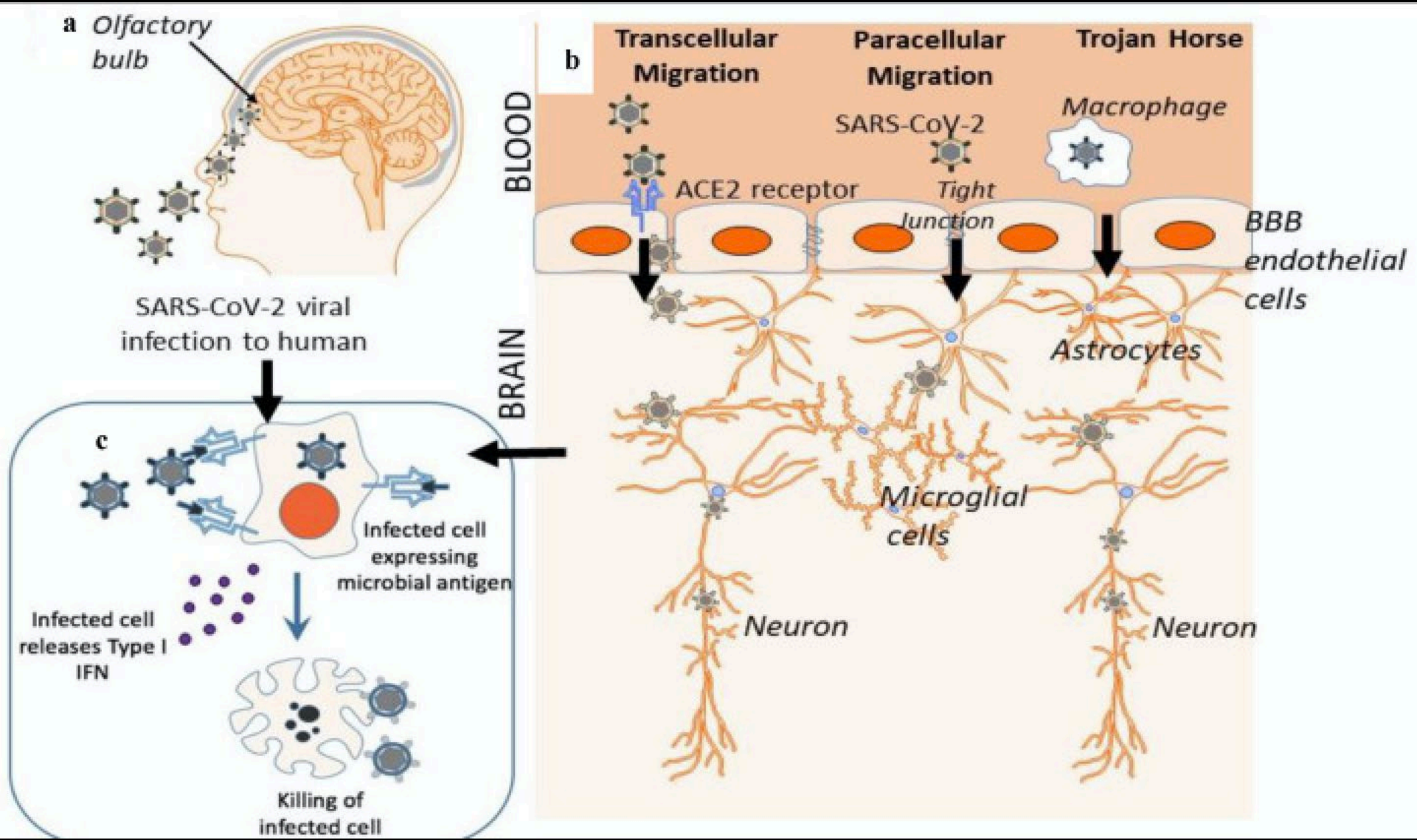


HOW DOES SARS-COV-2 ENTER THE CNS

- ACE2 is expressed in human olfactory epithelium and COVID-19 virus exploits the ACE2 receptor to gain entry inside cells
- SARS-CoV-2 present in the nasal endothelium may adhere to proteins along sensory and olfactory nerves to the brain .Evidence of this pathway includes loss of smell .
- ACE2 receptors are expressed in glial cells and neurons, which makes them a potential target of COVID-19.
- Previous studies have shown the ability of SARS- CoV to cause neuronal death in mice by invading the brain via the nose close to the olfactory epithelium

SARS-COVI-2 ENTERS THE CNS (CONT)

- The presence of the COVID-19 virus in the general circulation enables it to pass into the cerebral circulation where movement of blood within the microcirculation could be one of the factors that may facilitate the interaction of the COVID-19 virus spike protein with ACE2 expressed in the capillary endothelium.
- Subsequent budding of the viral particles from the capillary endothelium and damage to the endothelial lining can favor viral access to the brain .



INFECTION LEADS TO CYTOKINE STORM ON THE BLOOD-BRAIN BARRIER AND MALFUNCTION OF THE IMMUNE SYSTEM

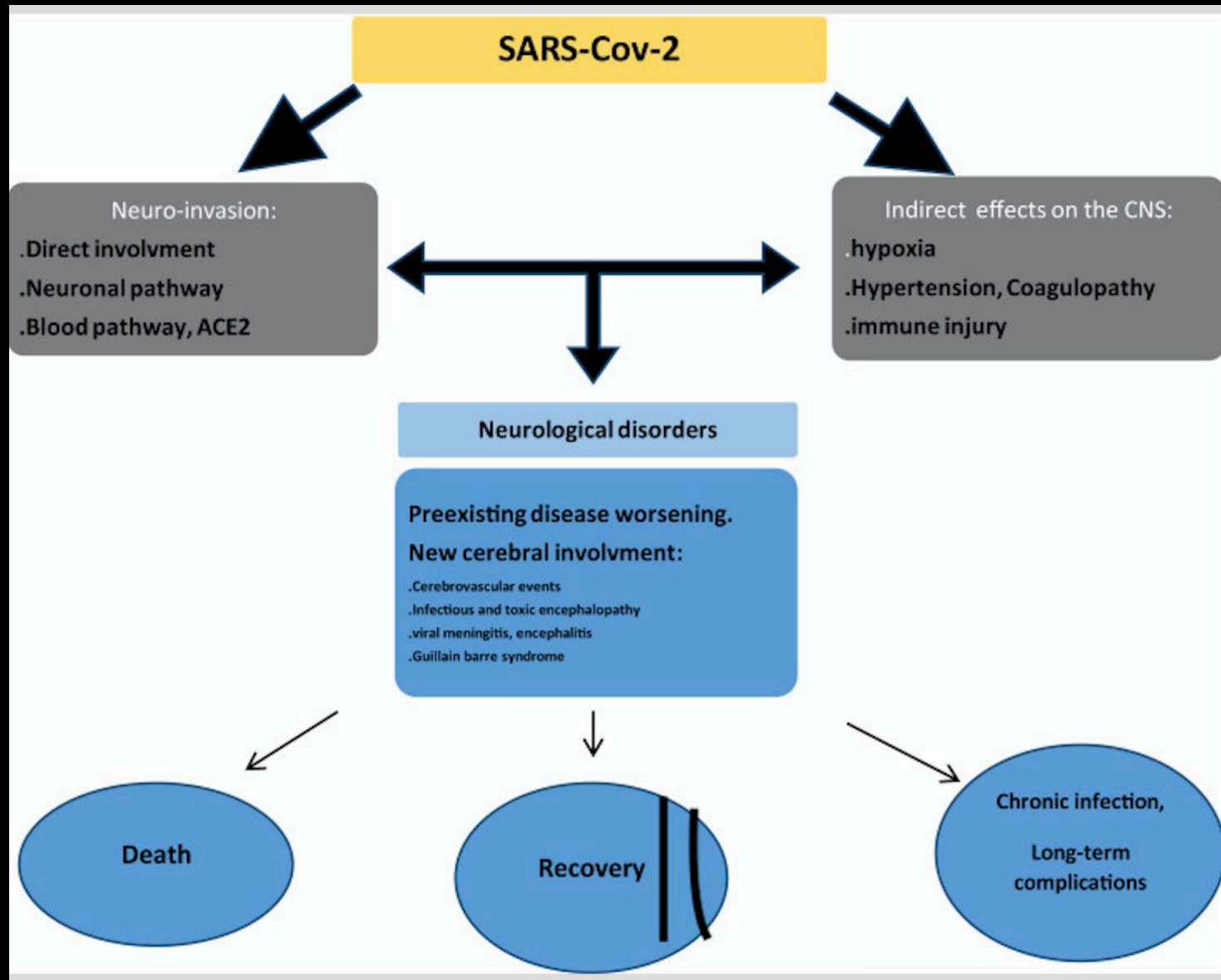
- Cells infected with SARS-CoV-2 may produce type I interferons, cytokines that alert the immune system to the presence of pathogen and induce an antimicrobial state in neighboring cells
- severe infection of SARS-CoV-2 often triggers an overproduction of pro-inflammatory cytokines, deemed the “cytokine storm”
- To date, several studies have reported increased levels of cytokines concurrent with SARS-CoV-2 infection; for example, levels of pro-inflammatory cytokines TNF- α , IFN- γ , and IL-6
- IL-6, in particular, has been documented for its potent role in immune dysregulation in COVID-19 . In the CNS, IL-6 is expressed primarily by astrocytes and microglia and is upregulated during CNS infection and neuroinflammation
- Prior studies have demonstrated that IL-6 may affect BBB integrity

Table 1. Key cytokines involved in COVID-19 cellular invasion and function in the immune system.

Cytokine	General Functions
Pro-inflammatory	
Tumor necrosis factor alpha (TNF- α)	Activation of neutrophils and platelets; enhances macrophage and natural killer cell effector function; anti-malignant cell cytotoxicity; necrosis and apoptosis [60].
Interferon gamma (IFN- γ)	Th1 cell differentiation; activation of macrophages; upregulation of class I and II major histocompatibility complex and antigen presentation; specific cytotoxic immunity; induction of antiviral enzymes; cell growth inhibition [61].
Interleukin-2 (IL-2)	T cell proliferation; long-term survival of T cells; development of T regulatory cells; NK cell growth factor; enhances NK cell cytotoxicity; antibody secretion; upregulation of B cell heavy and light chain gene expression [62].
Interleukin-6 (IL-6)	T cell growth; CD8+ T cell proliferation; differentiation of macrophages, megakaryocytes, and osteoclasts; stimulation of B cells to produce immunoglobulins [63].
Interleukin-8 (IL-8)	Recruitment and activation of neutrophils, increased expression of adhesion molecules; wound healing (stimulates migration and differentiation of fibroblasts); enhances metabolism of reactive oxygen species [64].
Anti-inflammatory	
Interleukin-4 (IL-4)	Th2 cell differentiation; immunoglobulin class switch to IgG1 and IgE; activation of alternative macrophages [65].
Interleukin-10 (IL-10)	Inhibition of pro-inflammatory cytokine production; downregulation of MHC molecules; B cell, mast cell, and thymocyte growth factor [66].

CAN CORONA VIRUSES DIRECTLY INFECT THE CNS? 2 EARLY CASES CONFIRMED THIS BUT NOT ALL BRAIN AUTOPSIES DID

- 11 month old boy with SVID s/p cord blood transplantation, presented with symptoms of encephalitis; brain bx confirmed presence of RNA sequence of human corona virus (2016)
- 24 y/o male presenting with headache and meningitis symptoms, and although nasal swab was negative for COVID-19, CSF PCR did confirm presence of SARS-COV-2
- At least 22 published autopsy series have looked at brain for presence of COV-2; about half were able to detect virus in CNS
- Many autopsies revealed evidence in the brain of lepto-meningeal inflammation, activation of microglia, microvascular thrombosis ,hypoxia, edema and necrosis



COMMON NEUROLOGICAL SYMPTOMS OF COVID-19 INFECTION

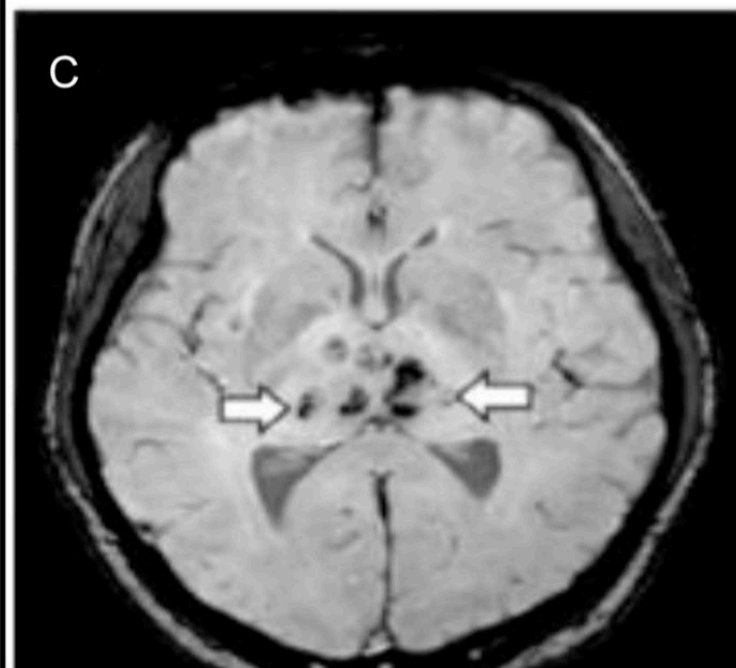
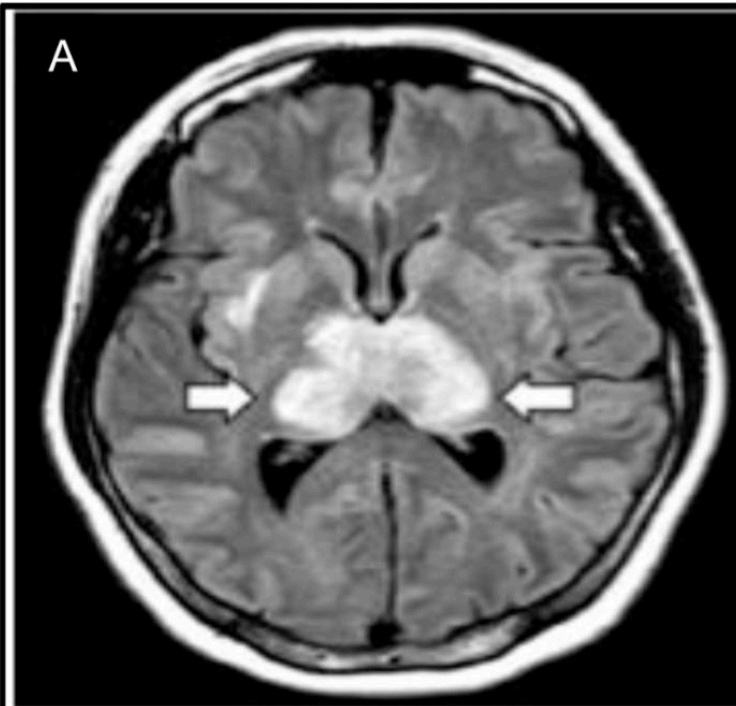
- One study documented that nearly 40% of patients acutely ill with COVID-19 had neurological symptoms
- Headache in over 40%
- Anosmia (over 80% in one study, olfactory epithelium enriched with ACE-2 receptors)
- Confusion
- Fatigue in over 65%
- Myalgias in over 45%
- Dysgeusia
- Dizziness

ACUTE NEUROLOGICAL SYNDROMES DESCRIBED IN SETTING OF COVID-19 SYSTEMIC INFECTION

- Encephalitis/meningitis
- Covid Encephalopathy
- Demyelinating disease: ADEM, transverse myelitis, acute demyelination syndromes
- Stroke, ischemic and hemorrhagic
- PRES
- Polyneuropathy, AIDP
- Pediatric neurological presentations

ACUTE NECROTIZING HEMORRHAGIC ENCEPHALOPATHY

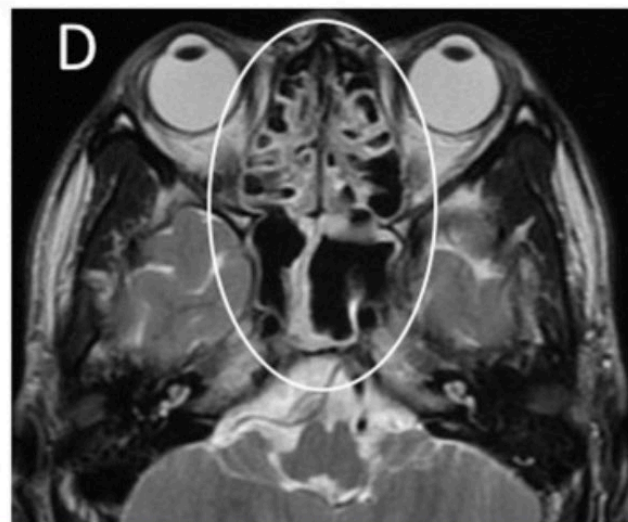
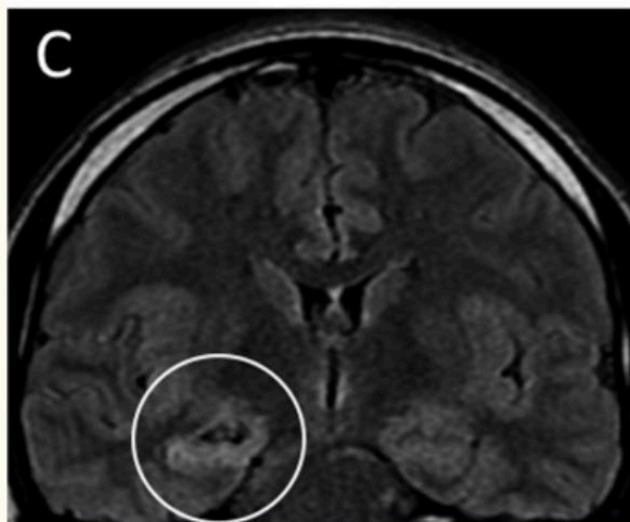
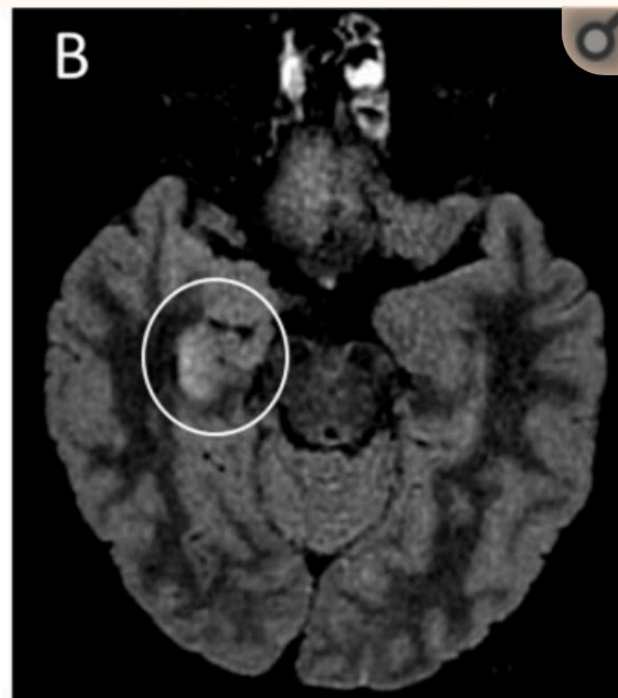
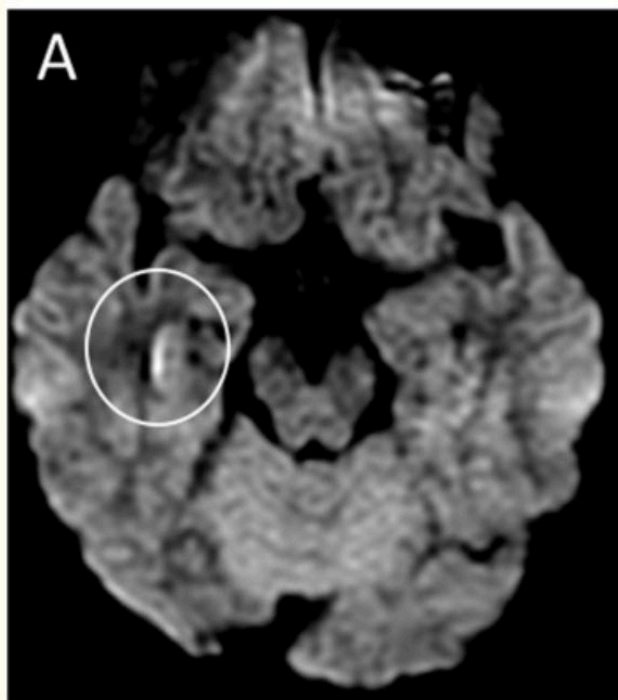
- 58 y/o female presented with confusion, cough and fever
- Non-contrast head CT images demonstrated symmetric hypoattenuation within the bilateral medial thalami and MRI demonstrated hemorrhagic lesions within the bilateral thalami, medial temporal lobes and sub insular regions



ENCEPHALITIS/MENINGITIS

- One of the first cases of encephalitis was reported in a 24 y/o male in Japan in February 2020
- Presented initially with headache , stiff neck and progressed to unresponsiveness after one week
- Developed clinical seizures and ultimately intubated for Status Epilepticus
- CSF opening pressure was 320 mmH₂O; 12 monocytes and 2 neutrophils; no rbcs; CSF was positive for SARS-COV-2
- Diffusion weighted images (DWI) showed hyperintensity along the wall of inferior horn of right lateral ventricle. Fluid-attenuated inversion recovery (FLAIR) images showed hyperintense signal changes in the right mesial temporal lobe and hippocampus with slight hippocampal atrophy. Contrast-enhanced imaging showed no definite dural enhancement.

These findings indicated right lateral ventriculitis and encephalitis mainly on right mesial temporal lobe and hippocampus.



COVID ENCEPHALOPATHY

- Criteria for diagnosing Encephalopathy in patients with COVID-19 are not well established but often seen in critically ill patients in whom other entities have been excluded
- Helms et al. described agitated encephalopathy in 40% of their patients with COVID-19, all of whom were admitted in the ICU due to ARDS. More than half of these patients showed confusion of varying degrees, and 67% of cases demonstrated diffuse corticospinal tract signs.
- 13 underwent brain MRI, and 8 out of 13 showed evidences of leptomeningeal enhancement.
- CSF samples of all these patients were negative for SARS-CoV-2
- EEG obtained in 8 patients showed only non-specific findings

COVID ENCEPHALOPATHY CAN BE ASSOCIATED WITH PROLONGED COGNITIVE DEFICITS POST-HOSPITALIZATION

- Of the patients in that series who had been discharged at the time of the publication , 15 of 45 (33%) had had a dysexecutive syndrome consisting of inattention, disorientation, or poorly organized movements in response to command.
- A more recent study looking at 740 patients from Mt Sinai Health System registry found persistent cognitive impairment for several months after discharge, including impaired executive functioning and processing speed

MECHANISM? CYTOKINE-MEDIATED INFLAMMATION

- One group studied 3 COVID-19 adult patients who presented with akinetic mutism
- CSF PCR negative for COV-2; other causes excluded
- EEG showed diffuse slowing
- Responded to steroids , but COVID encephalopathy can also spontaneously resolve with supportive care
- These cases share some clinical features with immune effector cell- associated neurotoxicity syndrome as seen following CAR-T therapy, a kind of immunotherapy that can trigger cytokine release syndrome (CRS) and is treated with tocilizumab(anti IL-6)

NEUROPSYCHIATRIC SYMPTOMS IN 3 PEDIATRIC CASES WERE ASSOCIATED WITH INTRATHECAL ANTIBODY SYNTHESIS

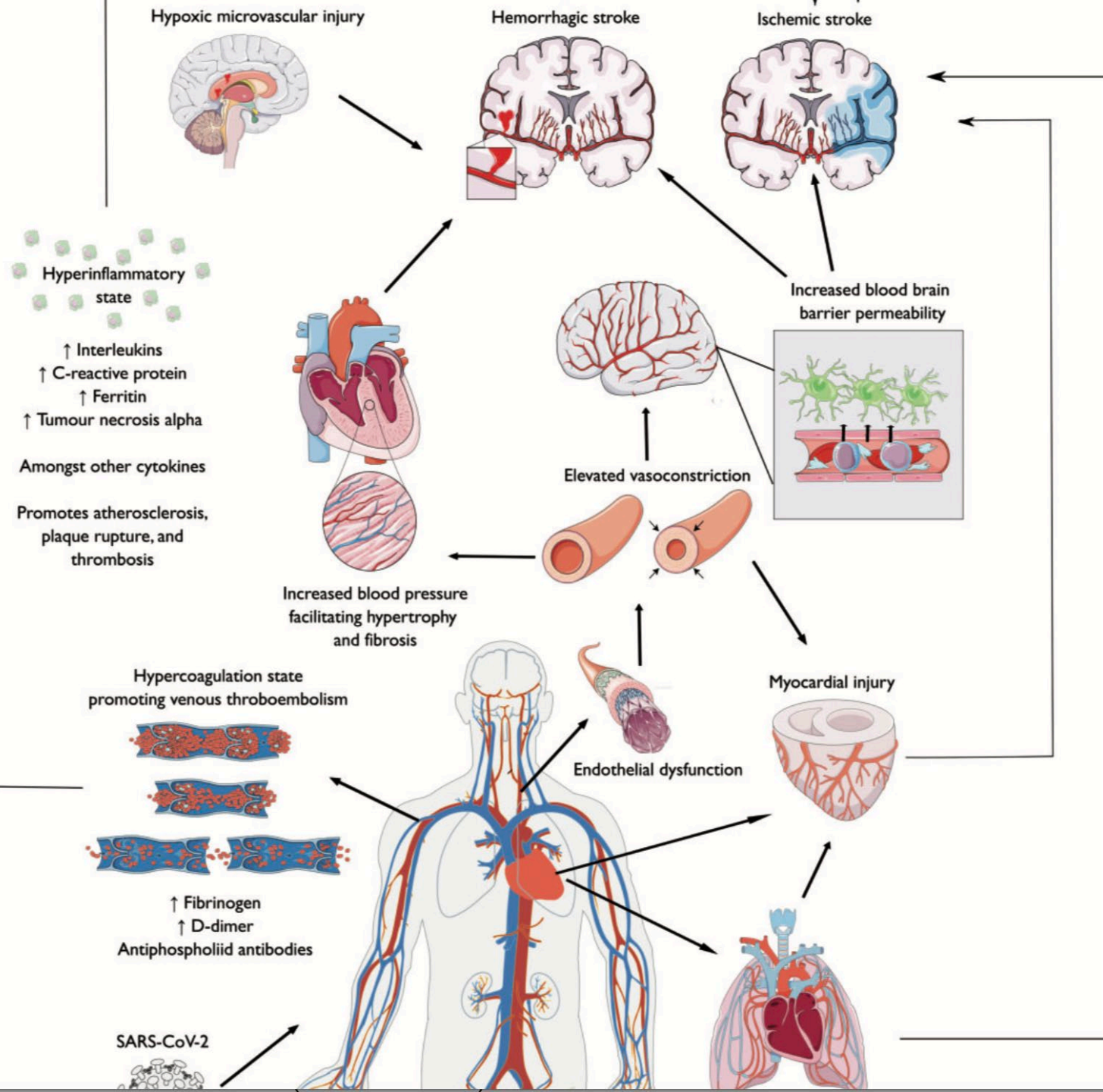
- UCSF recently published 3 cases of teenagers seen at their institution who had presented with acute onset mood lability, depression, anxiety, and OCD symptoms after exposure to Covid-19
- None had MIS-c (multi-system inflammatory syndrome in children)
- 2 were found to have CSF IgG against SARS-CoV-2 spike protein, receptor-binding domain, and nucleocapsid protein .
- All 3 had oligoclonal bands
- Treatment was with a combination of immunotherapy and psychiatric medications

STROKE: PRESENT IN 1.5 % OF PATIENTS WITH ACUTE COVID-19

- Large review and meta-analysis of over 108,000 patients with Covid-19 world –wide between December 2019 and September 2020
- 88% ischemic, hemorrhagic less common at 11%
- More common in individuals with pre-existing vascular risk factors ie HTN, DM, CAD
- Compared to individuals with stroke who did NOT have infection, patients with COVID-associated stroke were younger, had higher NIH stroke scale (av= 15) , more large-vessel occlusions and had higher in-hospital mortality
- Ischemic strokes were more likely cryptogenic and often multiple
- Over 60% were associated with severe infection, almost 90% had pneumonia

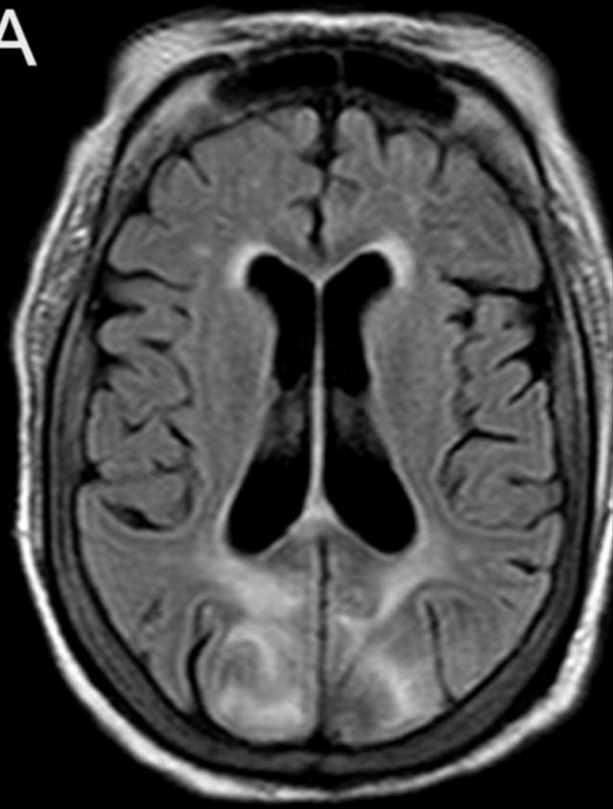
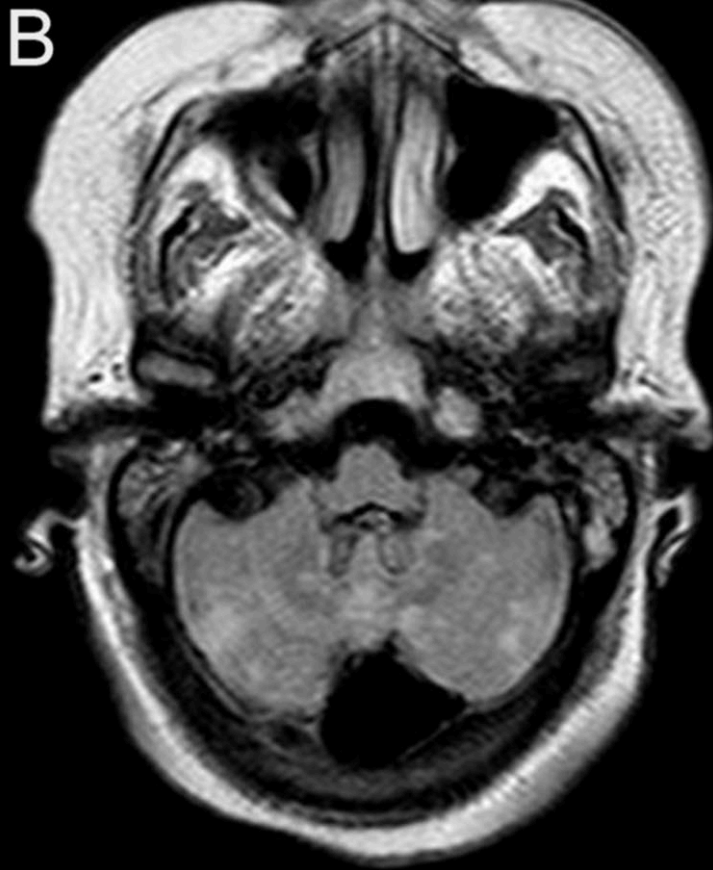
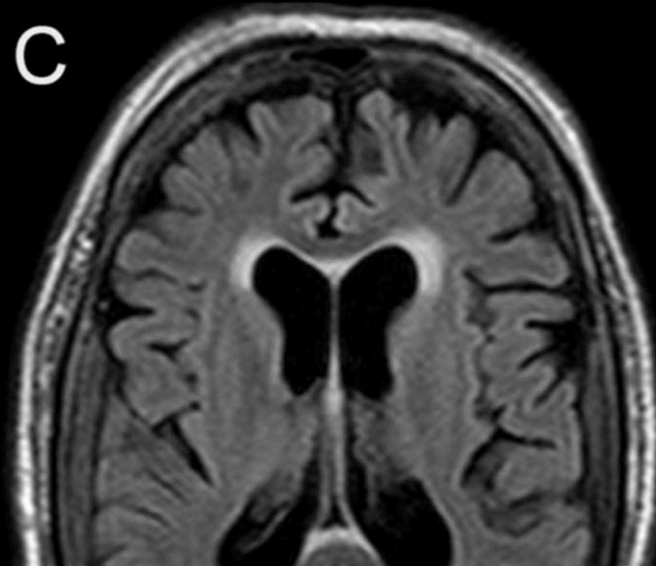
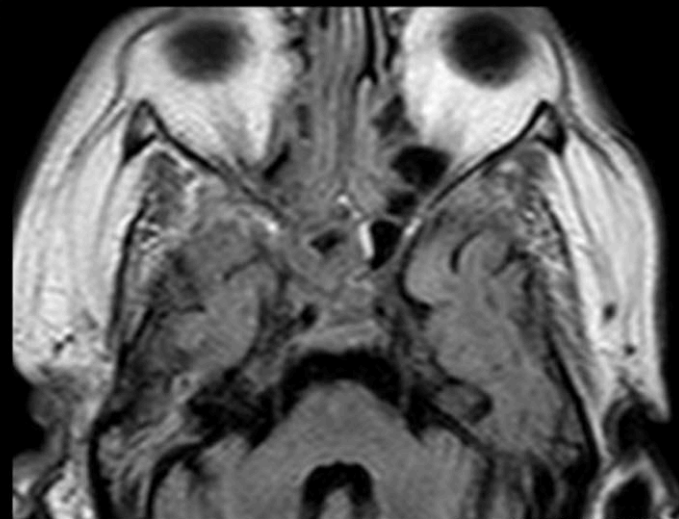
MECHANISMS OF ISCHEMIC STROKE IN COV-2 ARE MULTIFACTORIAL

- Activation of the coagulation pathway with elevated D-dimer and fibrinogen is a common feature of many individuals with severe COVID-19 infection , “sepsis induced coagulopathy”
- the presence of anti- phospholipid (aPL) antibodies, including IgA anticardiolipin antibodies and IgA and IgG beta 2 glycoprotein I antibodies, has been reported in severely infected patients with multiple cerebral infarcts.
- ACE receptors are expressed in vascular endothelium; direct viral invasion of endothelial cells causes an inflammation or “endothelitis” which has been proposed as one of the substrates for the thrombotic complications of COVID- 19.



POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES) IN COVID-REVIEW

- The key difference between PRES associated with COVID-19 and PRES in other settings appears to be the similar to mildly higher rate of hemorrhage, while the rate of restricted diffusion is approximately the same.
- Average age was 57
- CSF often normal
- Characteristic presentation similar to non-Covid: HTN, visual changes, altered mental status and seizures
- Most required mechanical ventilation

A**B****C****D**

DEMYELINATING SYNDROMES OFTEN IN COMBINATION

- Acute Transverse myelitis (ATM)
- ADEM- acute disseminated encephalomyelitis
- NMOSD - neuromyelitis optica spectrum disease
- Anti MOG IgG antibodies reported in some cases

ACUTE TRANSVERSE MYELITIS (ATM) CASE SERIES

- Review of 43 cases from 21 countries between March 2020 to January 2021
- All patients had typical features of ATM , with acute onset of paralysis, sensory level and sphincter defects due to spinal cord lesions seen on imaging
- Ages 21-79; 53% male and 47% female
- 70% had longitudinally extensive ATM involving 4 or more spinal cord segments
- Acute disseminated encephalomyelitis (ADEM) co-existed in about 20%, more often in women
- 3 were associated with optic neuritis and Neuromyelitis Optica (NMO)
- 2 were associated with acute motor axonal neuropathy (AMAN)

G U I L L A I N - B A R R E S Y N D R O M E (G B S)

- Systematic review of 73 cases in the literature
- COVID-19-associated GBS presented typically as acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and, to a lesser extent, with acute motor axonal neuropathy (AMAN)and acute motor sensory axonal neuropathy (AMSAN)
- Rare variants like Miller Fisher syndrome were also reported
- In analogy to classic GBS, approximately one-fifth of COVID-19-associated GBS subjects required mechanical ventilation during hospitalization
- More than 70% of patients showed a good prognosis, mostly after treatment with intravenous immunoglobulin.
- Patients with less favorable outcome were associated with a significantly older age in accordance with previous findings regarding both classic GBS and COVID-19. COVID-19-associated GBS seems to share most features of classic post-infectious GBS and possibly the same immune-mediated pathogenetic mechanisms

NEUROLOGICAL SEQUELAE OF COVID-19 IN CHILDREN

- Most of the literature has focused on adults but about 8% of cases involve children
- 1/3rd of pediatric cases experience headaches with acute Covid infection
- Predominant presentation is MIS-C: multi-system inflammatory syndrome, and can be associated with headache, seizures , encephalopathy, demyelinating disorders and aseptic meningitis
- The incidence of Covid-19 in children presenting with febrile seizures is less than 10% and may represent co-infection with other viruses.
- Acute flaccid myelitis (AFM) more typically associated with enteroviruses has only been reported in one child thus far with SARS-COV-2
- Kawasaki disease predominantly affects children under five years old and is characterized as an acute inflammatory process in small and medium caliber vessels , associated with cardiac involvement and a greater inflammatory response with macrophage activation

COVID-19 NEUROLOGIC SEQUELAE IN CHILDREN : DEMYELINATING SYNDROMES ALSO SEEN

- Guillain-Barre
- Acute transverse myelitis
- ADEM
- Anti- MOG syndromes (myelin oligodendrocyte glycoprotein) with blindness and spinal cord lesions as well as encephalitis

IMPACT OF COVID-19 INFECTION ON NEUROLOGICAL DISORDERS

- Studies thus far have shown “unmasking” of incipient neurological conditions such as Alzheimer’s
- At least one study has shown worsening of pre-existing primary headache disorders after COVID-19 infection
- Treatments of some neurological conditions may predispose to more severe disease and poor vaccination response ie B cell therapies in Multiple Sclerosis and related disorders
- Medication used to treat neurological conditions may be protective: ie use of amantadine in Parkinson’s disease and MS in one prospective study

IMPACT ON PARKINSONS DISEASE

- Review of 141 Parkinson's disease patients from Lombardy, Italy; mean age 65, duration 6 yrs
- 12/141 developed Covid-19 disease (8.5 %)
- motor and non-motor symptoms significantly worsened in the Covid-19 group, requiring therapy adjustment in 1/3rd
- Clinical deterioration was explained by both infection-related mechanisms and impaired pharmacokinetics of dopaminergic therapy
- Urinary issues and fatigue were the most prominent non-motor issues
- None experienced autonomic failure

IMPACT OF COVID ON ALZHEIMERS DISEASE (AD): STUDIES ONGOING

- Experiments have shown that systemic, NLRP3 (macrophage)-mediated inflammation adversely affects beneficial immune functions in the brain and may trigger the pathological accumulation of neurodegeneration-associated peptides such as fibrillar amyloid- β
- Induction of the NLRP3 inflammasome can directly induce or aggravate neurodegenerative processes that lead to functional impairment in AD or strongly contribute to the spreading of pathology and thus the progression of the disease
- Other researchers are investigating the link between ACE-2 (RAS) and A β in SARS-CoV-2 affected patients to see if there are genetic risks for unmasking of Alzheimer's with SARS-COV-2 infection

MS AND COVID-19



COVID-19 Infections in MS & Related Diseases



This COViMS (COVID-19 Infections in MS & Related Diseases) is a joint effort of the National MS Society, the Consortium of MS Centers and the Multiple Sclerosis Society of Canada to capture information on outcomes of people with MS and other CNS demyelinating diseases (Neuromyelitis Optica Spectrum Disease, or MOG antibody disease) who have developed COVID-19.

COVIMS IS THE DATABASE FOR MS, NMO AND MOG DISEASE IN THE US

- 1626 patients included at last data release of COViMS
- Ambulatory disability and older age were each independently associated with increased odds of all clinical severity levels compared with those not hospitalized after adjusting for other risk factors
- Overall mortality was 3.3 %
- Older age, obesity, and several cardiovascular comorbidities were associated with more severe COVID-19
- www.covims.org

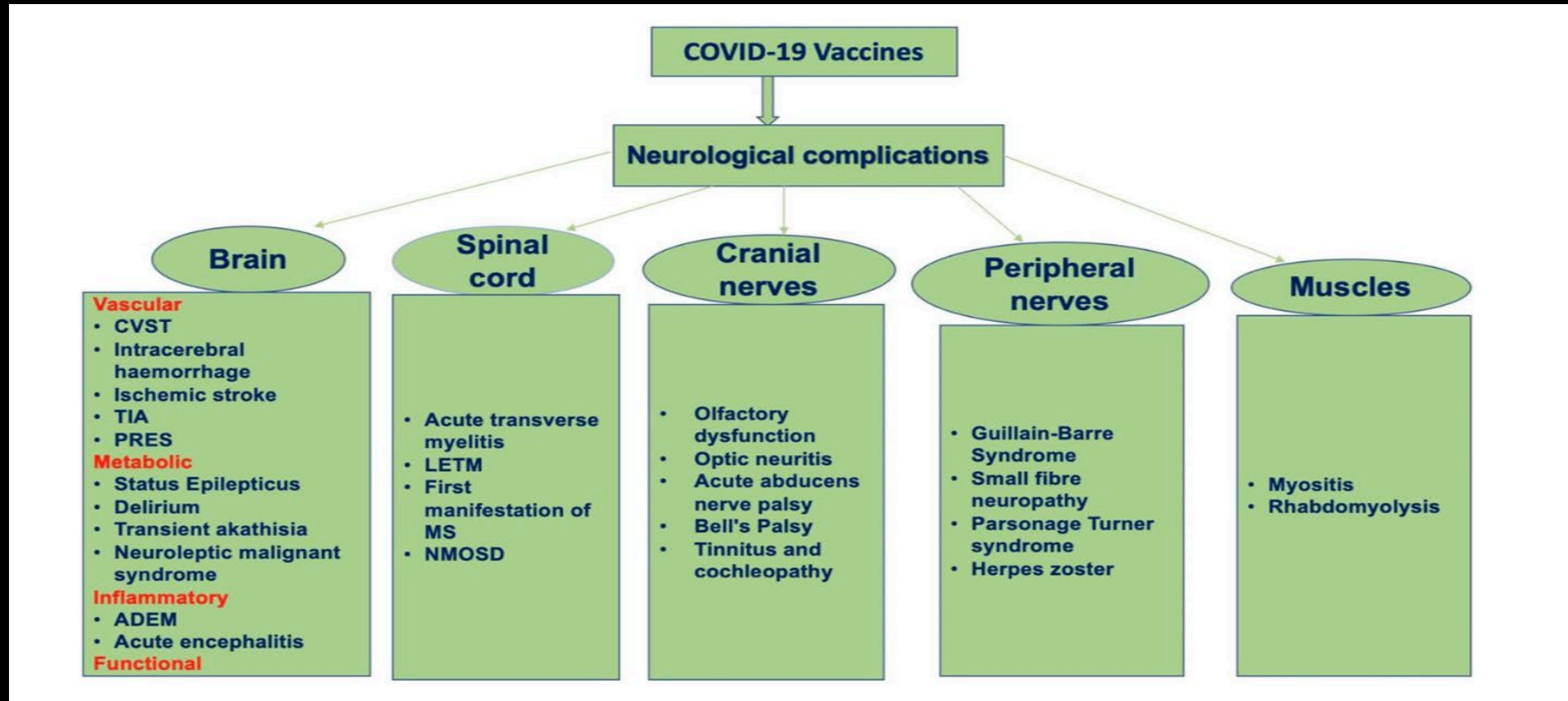
HOW TO PREVENT NEUROLOGICAL COMPLICATIONS OF COVID-19

- December 11, 2020, the FDA issues EUA for Pfizer BioNTech COVID-19 mRNA vaccine
- December 18, 2020 the FDA issued EUA for Moderna COVID-19 mRNA vaccine
- February 27, 2021 the FDA issued EUA for Janssen COVID-19 adenovirus (viral vector)vaccine

IMPACT OF MRNA COVID VACCINATION ON CNS

- Mostly very good news: recent study from Israel of 702 patients with known history of Guillain Barre between 2000 and 2020 were identified; 539 had 2 doses
- 5 had some neurological complaints (seizure, pre-existing tremor, paresthesia)
- 1 had sensory-motor symptoms and electrodiagnostic evidence of relapse, was treated with plasma exchange and responded with mild proximal weakness at time of discharge

LARGER WORLD-WIDE REVIEW OF NEUROLOGICAL COMPLICATIONS AFTER COVID VACCINATION



CONSIDERING THE ENORMITY OF RECENT COVID-19-VACCINATED POPULATION, THE NUMBER OF SERIOUS NEUROLOGICAL EVENTS IS SMALL

- The most devastating neurological post-vaccination complication is cerebral venous sinus thrombosis. Cerebral venous sinus is typically reported in females of childbearing age, generally following adenovector-based vaccination
- Findings in a series of 23 patients noted association of thrombocytopenia and thrombosis 6-24 days after adenovirus vaccine
- Many had elevated D-Dimer and antibodies to platelet factor 4

DEMYELINATING SYNDROMES POST-VACCINATION

- ADEM and ATM have been seen, more commonly with adenovirus vaccines
- In some cases these events have been associated with finding of antibodies to AQ-4 and new diagnosis of NMO
- Reports of good response to methylprednisolone and IVIG
- Acute Guillain-Barre more common with adenovirus vaccine; average onset 2 weeks after vaccination and many adults present with only facial diplegia

HEADACHE FOLLOWING COVID-19 VACCINATION: COMMON- RED FLAG WARNING

- Seen in 40% of recipients of adenovirus vaccine (J and J)
- Common with mRNA vaccines, especially after dose #2
- Delayed onset of headache following an adenovirus vector-based COVID-19 vaccine is associated with development of Cerebral Venous Thrombosis (CVT)
- Patients with new-onset headache, 1 week after vaccination with an adenovirus vector-based vaccine, should receive a thorough clinical evaluation and CVT must be ruled out.

IMPACT OF TREATMENT OF COVID ON CNS: ECMO USED IN APPROXIMATELY 3% OF PATIENTS

- Neurological complications of ECMO: extra-corporeal membrane oxygenation
- Used in previous respiratory outbreaks MERS, H1N1, SARS and now for COVID-19
- In 44 studies, the median frequency of acute neurologic complications is 13% (5% intracranial hemorrhages, 5% ischemic strokes, 2% seizures).
- Neurologic complications are reported more frequently with veno-arterial ECMO compared with veno-venous ECMO
- Median in-hospital mortality is higher with neurologic complications
- Risk factors are age, pre- ECMO cardiac arrest, hypoglycemia, and administration of inotropes
- Studies emphasize importance of daily weaning from sedation and neuromuscular blockers for neurologic assessment and coagulation monitoring

LONG COVID SYNDROME

- Long-Haul COVID Avindra Nath, MD
Neurology® 2020;95:559-560.
doi:10.1212
- As Neuro-immunologists, we may be asked about these syndromes and management

WHAT IS LONG COVID?

- Persistent Symptoms lasting 4 -12 weeks after acute infection with SARS-CoV-2 Virus
- October 2021 WHO announced the first official definition of what constitutes Long Covid, or post-COVID-19 condition
- PASC occurs in individuals with a history of probable or confirmed SARS-COV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis
- Common symptoms include fatigue, shortness of breath , cognitive dysfunction but also other symptoms which may have an impact on daily functioning
- Symptoms may be new onset after initial recovery or persist from the initial illness
- Symptoms may also fluctuate or relapse over time

SYMPTOMS OF LONG COVID SYNDROME OR PASC

- **Specific** to SARS-CoV-2 infection
 - Fatigue, brain fog, loss of smell / taste, palpitations,
 - Known as Post Acute Sequela of SARS-CoV-2 (PASC)
 - PASC = **Long COVID** = Long Haulers = Chronic COVID
- **Generalized illness related** to SARS-CoV-2 infection
 - Deconditioning, treatment side effects, psychological effects of isolation, bereavement

EPIDEMIOLOGY

- **COVID-19**

Global: over 240 million infected and 5 million deaths

US: 44 million infected and 700,000 deaths

OR: 344,000 infected and 4,000 deaths

- **Long COVID prevalence ranges from 10-30% of all Covid cases**

Global: 24 million; US: 4.4 million; OR: 34,000

Public health effects are significant

WHAT FACTORS ARE ASSOCIATED WITH AN INCREASED RISK OF LONG COVID AFTER COVID-19 INFECTION?

- Long COVID can occur regardless of severity of COVID-19 illness: most patients were never hospitalized
- Severe COVID-19 infection, > 5 symptoms during initial infection increased risk LC
- Prevalence of LC higher in females, adults with chronic conditions
- Highest Prevalence in ages 35-69
- Few studies examining differences in risk of LC by race/ethnicity/socioeconomic status

WHAT ARE THE CHARACTERISTIC SYMPTOMS?

- Fatigue
- Post-Exertional Malaise
- Brain Fog
- Palpitations / tachycardia
- Sleep disruption
- Loss of taste / smell
- Depression / Anxiety / PTSD
- Headache
- Breathing Pain
- Neuropathic pain
- Joint & muscle pain
- Loss of hair
- Diarrhea, constipation
- Many others

LONG COVID NEUROLOGIC SYMPTOMS

- “Brain fog”
- Fatigue and exercise intolerance
- Headache
- Muscle pain, similar to ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome)
- Sleep disturbances, insomnia
- dysgeusia, ageusia
- Autonomic symptoms ; POTS (postural orthostatic tachycardia syndrome)

WHAT CAUSES LONG COVID?

Viral-dependent mechanisms

- Direct toxicity of the virus
- Abnormal function of the immune system?
- Persistent inflammation (hyperinflammatory state)?
- Viral reservoir?

Viral-independent mechanisms

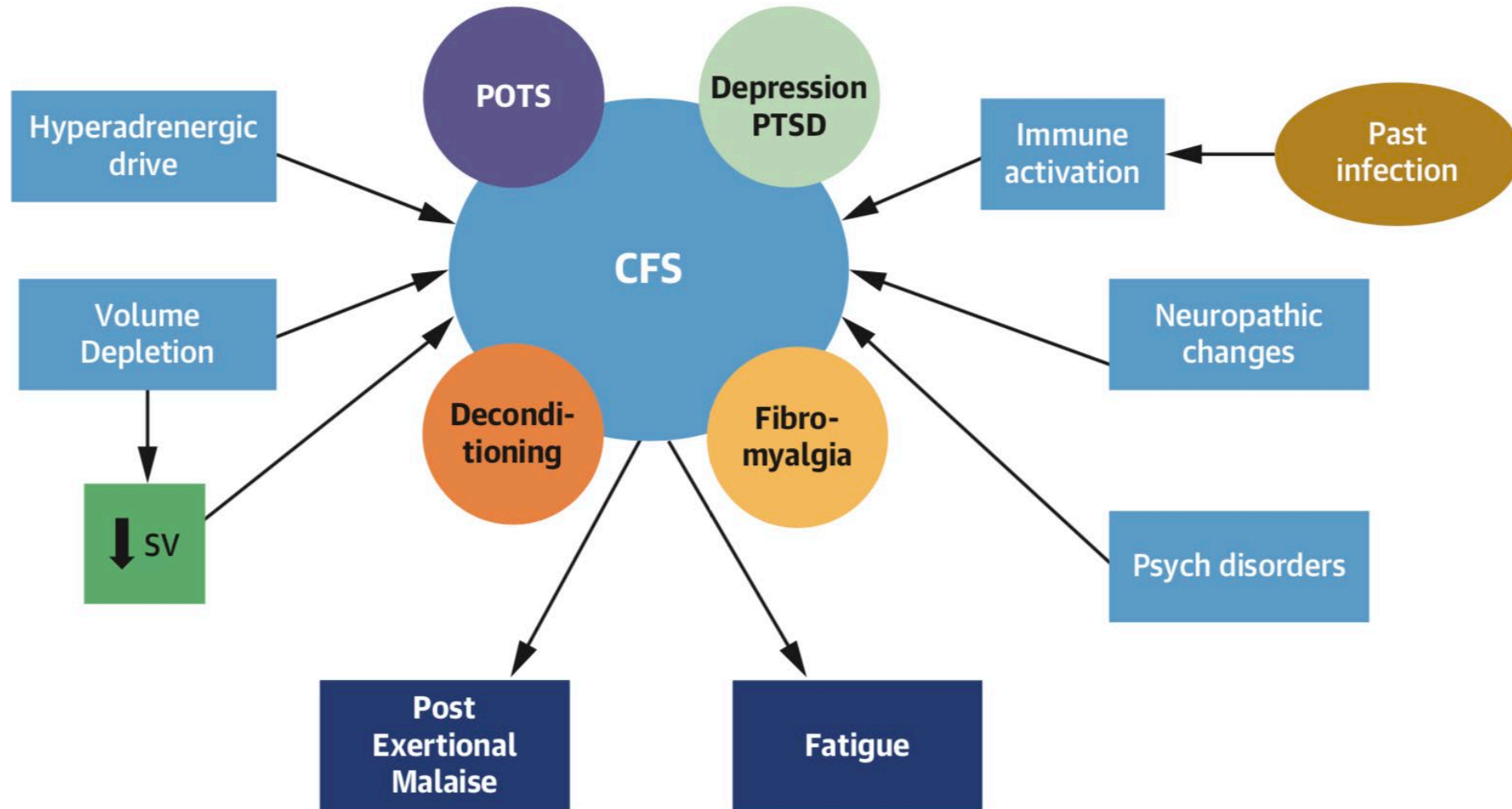
- Unmasking of conditions that were not yet detected?
- Pre-existing conditions can be worsened.

PARALLELS WITH OTHER CONDITIONS

POSSIBLE CONNECTIONS WITH POST-VIRAL
INFECTIONS ALSO SEEN IN SARS, MERS

- Fatigue & Post-exertional malaise: Chronic Fatigue Syndrome
- Brain Fog: Post-Concussion Syndrome (PCS)
- Hyperimmune reactions: Mast Cell Activation Syndrome
- GI problems– Irritable Bowel Syndrome (IBS)

CENTRAL ILLUSTRATION Symptomatic Schematic of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome



Natelson, B.H. et al. J Am Coll Cardiol. 2021;78(10):1056-1067.

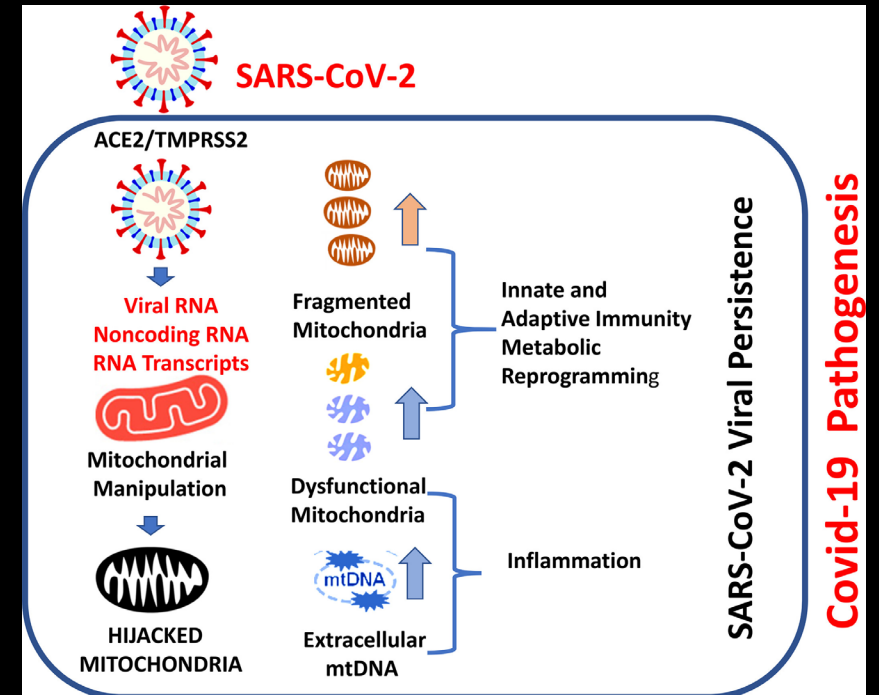
A symptomatic schematic of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). POTS = postural orthostatic tachycardia syndrome; PTSD = post-traumatic stress disorder; SV = stroke volume.

POSSIBLE MECHANISMS

- Unmasking of underlying co-morbidities
- Residual damage from underlying infection
- Persistent viral replication : SARS-COVI-2 has been isolated from CSF in a few cases
- Persistent immune activation : oligoclonal bands have been found in a few cases of severe COVID-encephalopathy, as well as persistent IL-6
- Nutritional lack: low Thiamine associated with persistent TH17 activation
- Widespread microglial activation

MITOCHONDRIAL DYSFUNCTION COULD BE AN IMPORTANT MECHANISM MULTI-SYSTEM IMPAIRMENT AFTER COVID-19

- SARS-CoV-2 targets mitochondria
Hijacked for viral replication
Decreases energy production
Decreases immune response
Increases inflammatory responses and reactive oxygen species



FDG- PET AND MASS SPECTROMETRY IN LONG COVID

FDG-PET IN LONG COVID

- ^{18}F -FDG brain PET hypometabolism in patients with long COVID
- European Journal of Nuclear Medicine and Molecular Imaging
- <https://doi.org/10.1007/s00259-021-05215-4>
- E. Guedj et al

18F-FDG BRAIN PET HYPO- METABOLISM IN PATIENTS WITH LONG COVID

- Methods: PET scans of 35 patients with long COVID were compared using whole-brain voxel-based analysis to a local database of 44 healthy subjects controlled for age and sex to characterize cerebral hypometabolism.
- PET abnormalities were evaluated in comparison with the patients' characteristics and functional complaints.

FDG BRAIN PET IN LONG COVID: RESULTS

- In comparison to healthy subjects, patients with long COVID exhibited bilateral hypometabolism in the bilateral rectal/orbital gyrus, including the olfactory gyrus; the right temporal lobe, including the amygdala and the hippocampus, extending to the right thalamus; the bilateral pons/medulla brainstem; the bilateral cerebellum (p-voxel < 0.001 uncorrected, p-cluster < 0.05 FWE-corrected).
- These metabolic clusters were highly discriminant to distinguish patients vs healthy subjects (100% correct classification).

FDG BRAIN PET IN LONG COVID

- These clusters of hypometabolism were significantly associated with more numerous functional complaints (brainstem and cerebellar clusters), and all associated with the occurrence of certain symptoms (hyposmia/anosmia, memory/cognitive impairment, pain and insomnia) ($p < 0.05$).
- In a more preliminary analysis, the metabolism of the frontal cluster which included the olfactory gyrus was worse in the 7 patients treated by ACE drugs for high blood pressure ($p = 0.032$), and better in the 3 patients that had used nasal decongestant spray at the infectious stage ($p < 0.001$).

FDG BRAIN PET IN LONG COVID

- In comparison to the 44 healthy subjects, the patients with long COVID presented with significant hypometabolism involving 4 clusters:
- bilateral rectal/orbital gyrus, including the olfactory gyrus
- right temporal lobe, including the amygdala and the hippocampus, extending to the right thalamus
- bilateral pons/medulla in the brainstem
- bilateral cerebellum

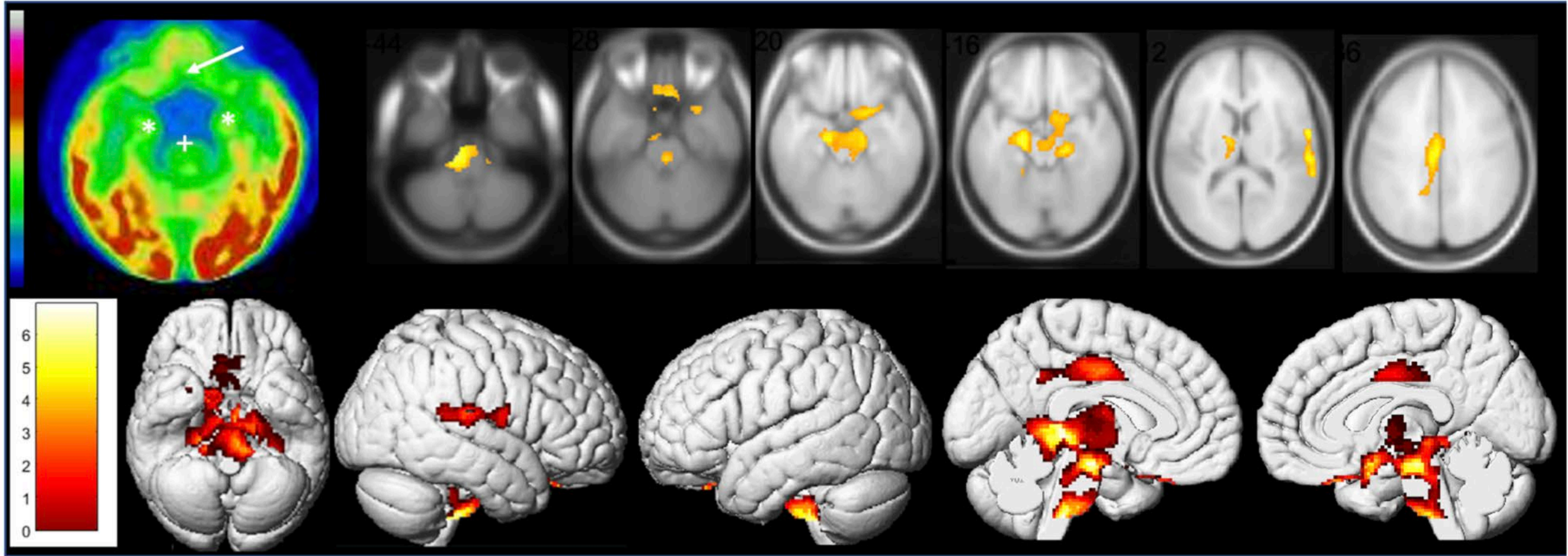


Fig. 2 Brain ^{18}F -FDG PET hypometabolism of the second patient. Bilateral hypometabolism of olfactory/rectal gyrus (white arrow), medial temporal lobe (white*), and brainstem (white+) is visually identified, and confirmed by whole-brain voxel-based SPM8 comparison to healthy

subjects (p voxel < 0.001 , p -cluster < 0.05 , uncorrected), also including the right pre-/post-central gyrus, the right superior temporal gyrus, bilateral thalamus, hypothalamus, and cerebellum

FDG PET IN LONG COVID

- This study demonstrates a profile of brain PET hypometabolism in long COVID patients with biologically confirmed SARS-CoV-2 and persistent functional complaints more than 3 weeks after the initial infection symptoms, involving the olfactory gyrus and connected limbic/paralimbic regions, extending to the brainstem and the cerebellum.
- Hypometabolic patterns correlated with patients' symptoms
- Findings may reinforce the hypothesis of SARS-CoV-2 neurotropism through the olfactory bulb and the possible extension of this impairment to other limbic/paralimbic structures as well as to the thalamus, the cerebellum, and the brainstem within these highly connected regions

MASS SPECTROMETRY IN LONG COVID

- Hypothesis was : Long Covid symptoms could be related to a lingering ‘tail’ and an abnormal inflammatory response to an infection, by a type of virus the body has not seen before.
- They applied the assay to a cohort of samples taken from healthcare workers who had tested positive for SARS-CoV-2 infection by PCR and were either asymptomatic or had only a mild infection.
- Samples were taken at least 40–45 days post infection and demonstrated a positive antibody test.
- Compared these with serum from healthcare workers with a negative antibody test, no reported infection and no positive PCR test.

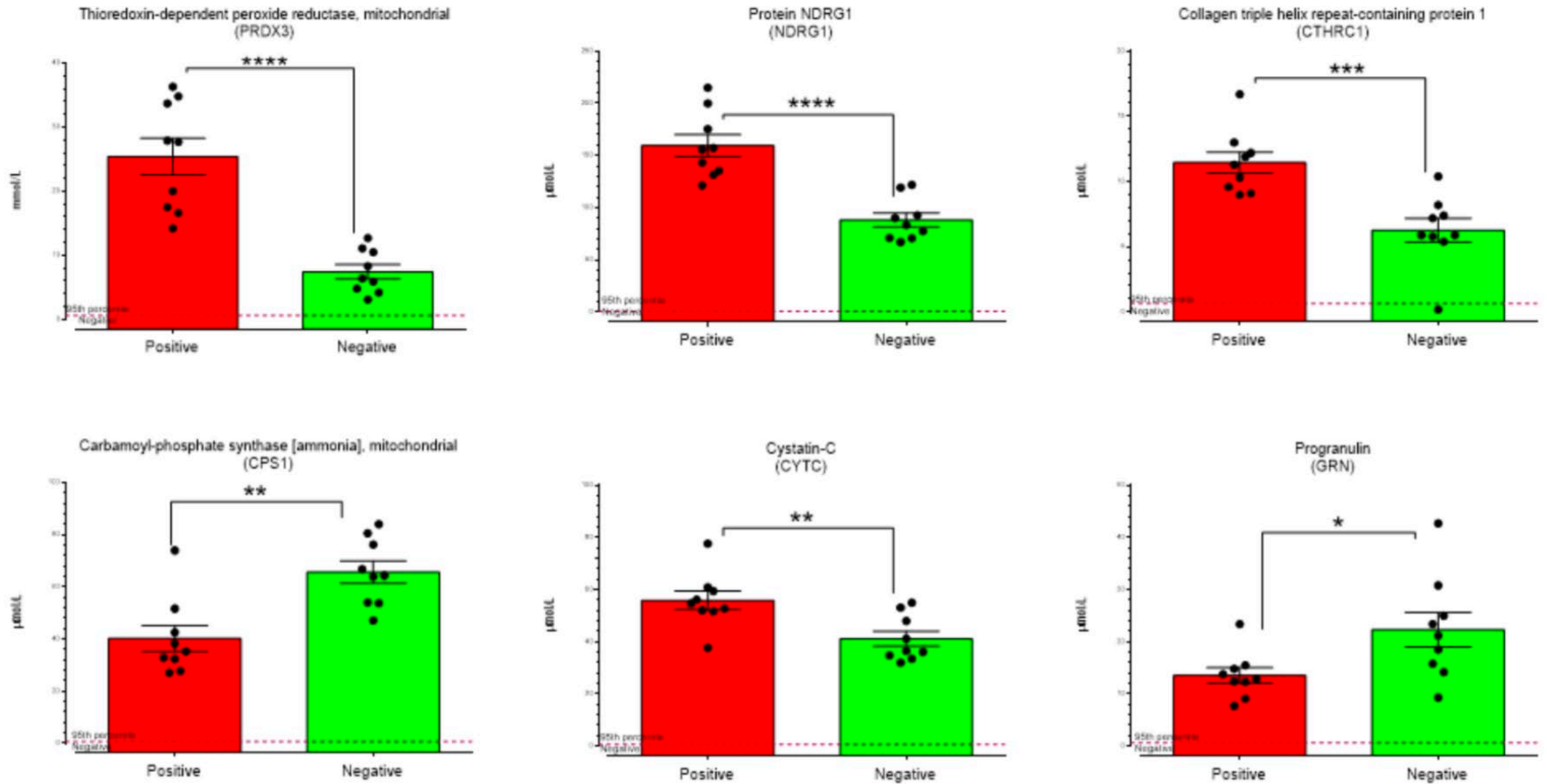


Figure 2. Altered proteins in post infection serum. Proteins significantly affected ($p < 0.001$) by non-parametric statistical analysis in the serum of >40 day post SARS-Cov-2 infected healthcare workers **** $p < 0.0001$, *** $p < 0.001$, ** $p < 0.01$, * $p < 0.01$.

SIGNIFICANCE OF THESE PROTEINS

- PRDX3: mitochondrial/antioxidant
- NDRG-1: stress response
- CTHRC1: angiogenesis, proliferation
- CPS1: mitochondrial
- Cystatin C: neurodegeneration, MS, NMO, MOG, controversial
- Progranulin: FTD


SIGNIFICANCE OF THESE FINDINGS IN LONG COVID

- patients who have suffered from an asymptomatic or mild SARS-CoV-2 infection, after 40 days post-infection still exhibit a significantly raised group of biomarkers involved in inflammation and the stress response.

DO THESE STUDIES TEACH US SOMETHING ABOUT LONG COVID?

- Involvement of deeper structures on FDG-PET could explain some of the more persistent behavioral, ANS and cognitive issues we see in Long Covid
- Longitudinal studies in both Mass Spectrometry and FDG- PET are needed to understand more about the pathphysiology of Long Covid neurological symptoms and possible mechanisms of neuroinflammation , and how these are similar and different from other inflammatory conditions such as MS

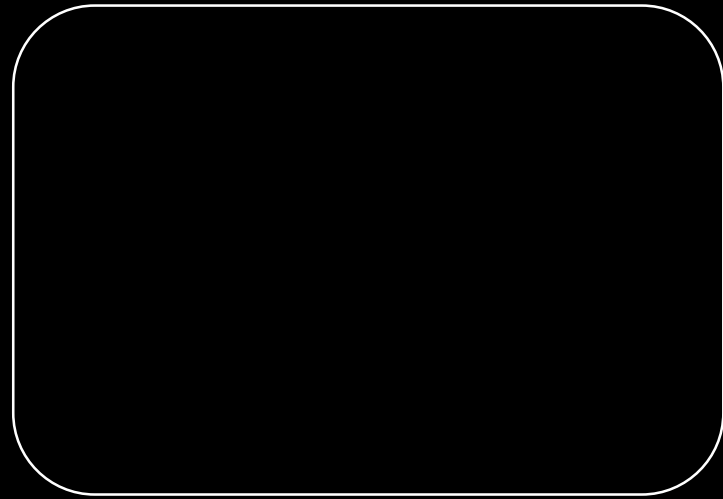
Evaluation and Management Of Long COVID



SOME PRINCIPLES FOR MANAGING LONG COVID: OHSU LONG COVID CLINIC APPROACH

- Chronic illness
- Resist injustices
- Care not Rescue
- Bio-Psycho-Socio-Ecological
- Care Team
- Crisis Planning
- Attention
- Representation
- Affiliation
- Improving function & quality of life
- Managing symptoms
- Multimodal

MANAGEMENT OF A CHARACTERISTIC SYMPTOM



Fatigue and
Post-Exertional Malaise

Common Signs and Symptoms

Pathophysiology

- Short of breath
- Feels weighed down by a lead weight
- Severe exhaustion after minimal exertion, with prolonged post-exertional malaise and recovery
- “Crash” after “good day”

Common Signs and Symptoms

Pathophysiology

- Multifactorial (mitochondrial dysfunction, mood, stress, deconditioning, autonomic dysfx, immune dysregulation, etc.)

Common Signs

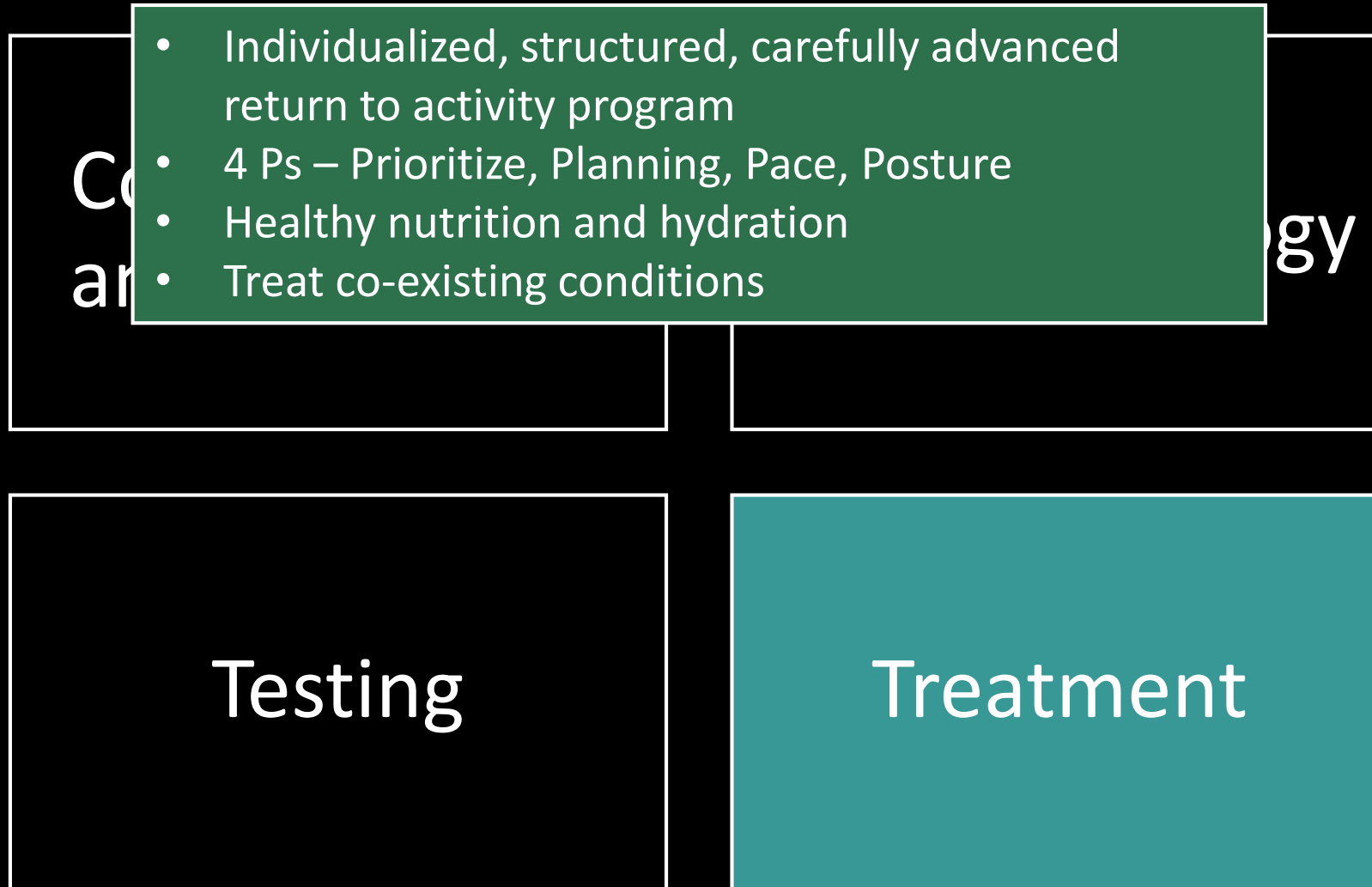
Pathophysiology

- Basic labs, CXR, EKG
- Level of Physical Activity Level
- Depression screening
- Assess sleep

Testing

Treatment

Fatigue and Post-exertional Malaise



RATIONALE BEHIND OUR OHSU PHYSICAL THERAPY PROGRAM

- **Not an ‘aerobic exercise’ program**
Individualize the optimal level of activity and exertion
Systematically advance the progression of activity
- **Recovery depends on**
A new focus and understanding of your breathing
Heart Rate
Knowing your limits and not pushing it

OHSU APPROACH EMPHASIZES COGNITIVE THERAPY FOR BRAIN FOG

- Speech Language Therapist
Initially 1x / week then biweekly
- Evaluate: Language, attention, memory, energy, sleep, other
- Monitor: Processing speed, word errors, metacognition
- Recommendation:
Individualized cognitive rehabilitation program
Also focus on sleep, diet, exercise, brain / body connection

**DYSAUTONOMIA IN LONG COVID
PATIENTS: SIGNIFICANT IMPACT TO
QUALITY OF LIFE**



**DYSAUTONOMIA INTERNATIONAL
9TH ANNUAL CONFERENCE**

**PARTNERING FOR
PROGRESS**

JULY 15-18, 2021

AUTONOMIC DYSFUNCTION IN LONG COVID: ORTHOSTATIC INTOLERANCE

- Common in Long Covid patients
- Often younger, in one series 26-50 , high % female
- Orthostatic hypotension (OH)
- vasovagal syncope (VVS)
- Postural orthostatic tachycardia syndrome (POTS): HR > 30 bpm within 10 minutes upright +sx
- Etiology unclear, may be mediated by autoantibodies triggered by COVID infection to alpha or beta adrenoreceptors or muscarinic receptors
- Interestingly not common in PD patients after COVID infection

MANAGEMENT OF ORTHOSTATIC INTOLERANCE POST COVID-19

- Tilt table: OHSU has capacity, thanks to our electrophysiology division
- Education
- Exercise program (see OHSU PT)
- Fluid and Salt replacement
- Avoid triggers ie prolonged standing
- Isometric exercises –use as counter measures
- Compression garments
- Pharmacological treatment: stop norepi reuptake inhibitors (duloxetine, nortrip); fludrocortisone helps with hypovolemia, midodrine also effective; propranolol can attenuate palpitations

LONG-COVID POTS: AAS STATEMENT

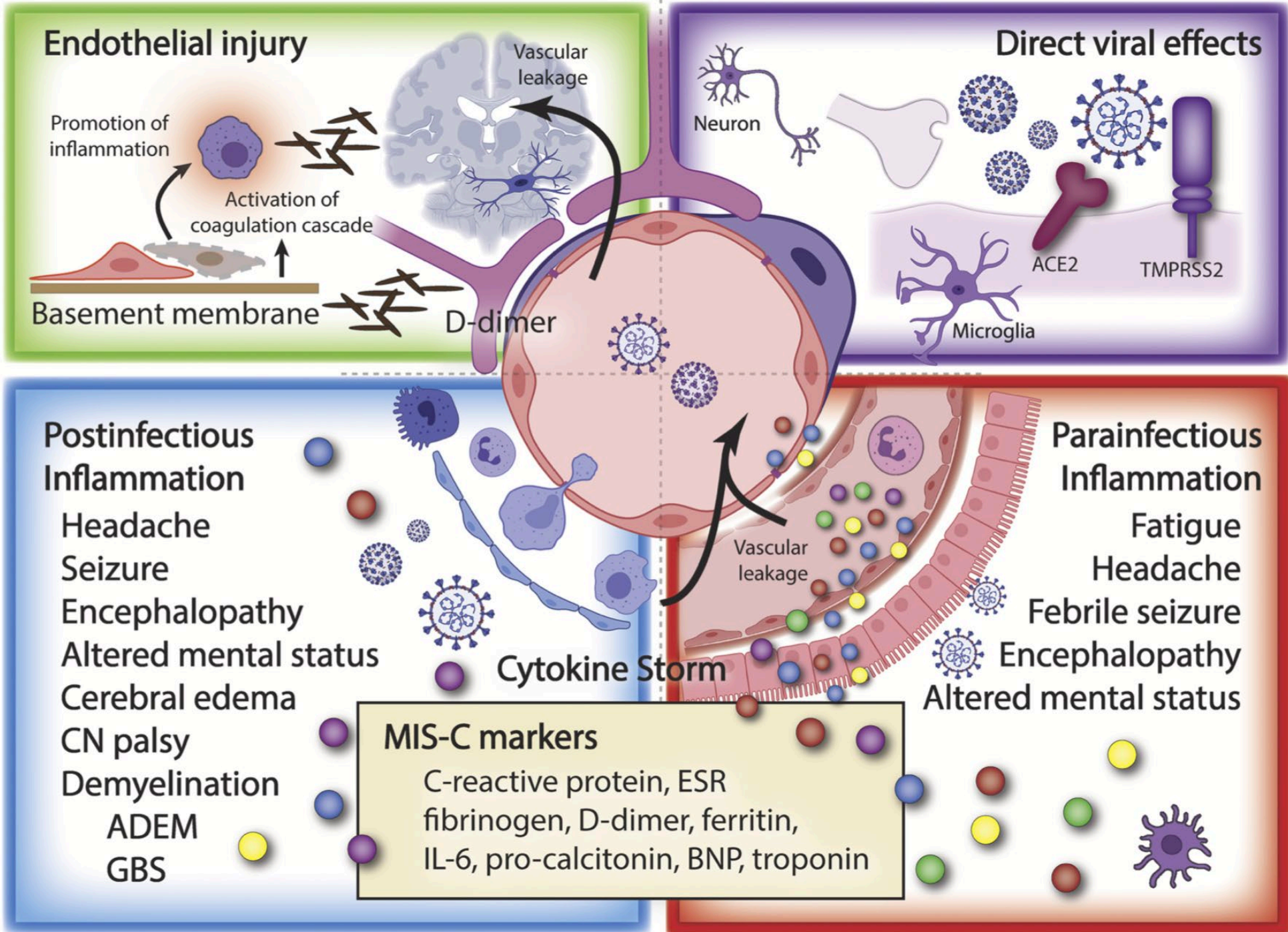
- The American Autonomic Society has provided a statement of need to guide physicians
- The number of physicians familiar with care of POTS is insufficient for the patient volume anticipated
- Will likely require increased infrastructure and for providers to start caring for these patients outside of specialty centers
- Treatment protocols need to be shared
- These patients will need more visits with our allied health professionals to deliver the needed care: this will take commitments from hospitals to address
- Additionally, several research opportunities exist : what is the natural hx, pathophysiology, best practices?

CLINICAL TRIALS.GOV

- Over 150 trials for Long Covid currently listed
- Many include PT/Rehabilitation approaches
- Some are looking at repurposed old medications: cetirizine and famotidine (UW protocol), LDN
- Others are actively studying new small molecules
- Supplements such as CoQ10 high dose (500mg /day)
- Hyperbaric Oxygen

LONGER TERM CONCERNS

- Still not known if SARS-COV-2 remains in immunologically privileged sites, such as the brain or the eye, similar to measles virus which can remain latent , and in settings of immunosuppression, reactivate and precipitate SSPE (sub-acute sclerosing panencephalitis)
- As of now, we understand a little more of the immediate and post-infectious consequences of infection with SARS-Cov-2 infection, much of which relates to host immune response
- Induction of the NLRP3 inflammasome can directly induce neurodegenerative processes that lead to functional impairment in AD or strongly contribute to the spreading of pathology and thus the progression of the disease
- Recent findings that NLRP3-driven modulation of phosphokinases and phosphatases which largely account for the formation of neurofibrillary tangles in murine models of tauopathy raises the concern that COVID-19 patients may experience an induction of



THANK YOU

- Dr. Juliette Preston, Dr. Aluko Hope, Dr. Eric Herman and the OHSU Long Covid Task Force
- OHSU General Neurology group seeing Long Covid patients, especially Dr. Andrew Natanson and Dr. Michael Lane
- Dr. Peter Spencer – Marquam Hill Lecture series and for bringing attention to this topic