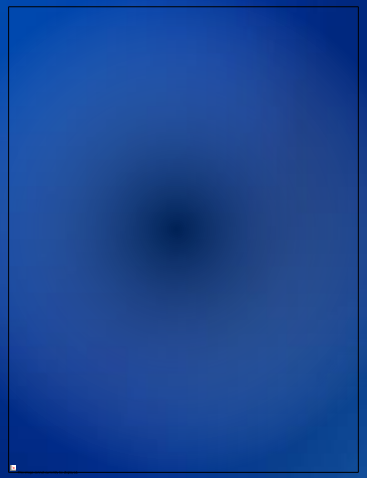
Neurological Complications of Coronavirus Disease 19 (COVID-19)

Dr. Mohammad Yazdchi

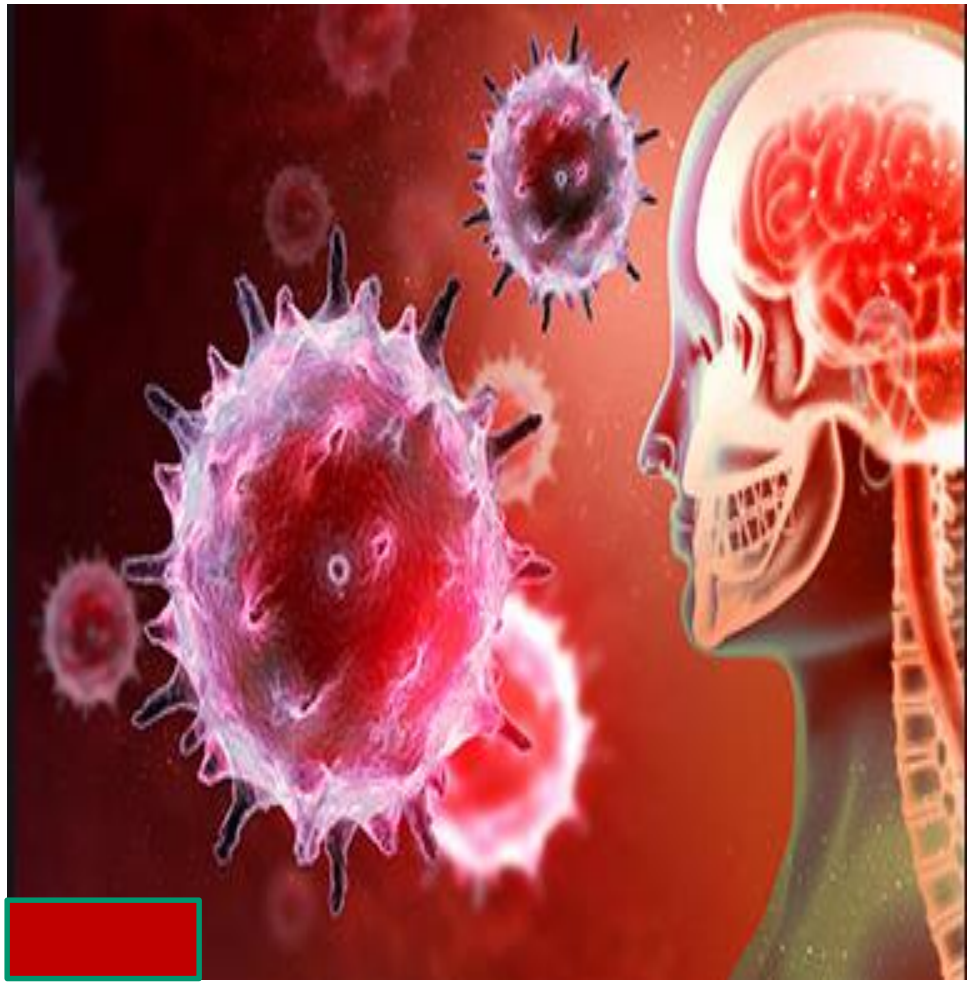
Professor of Neurology

Tabriz university of medical science

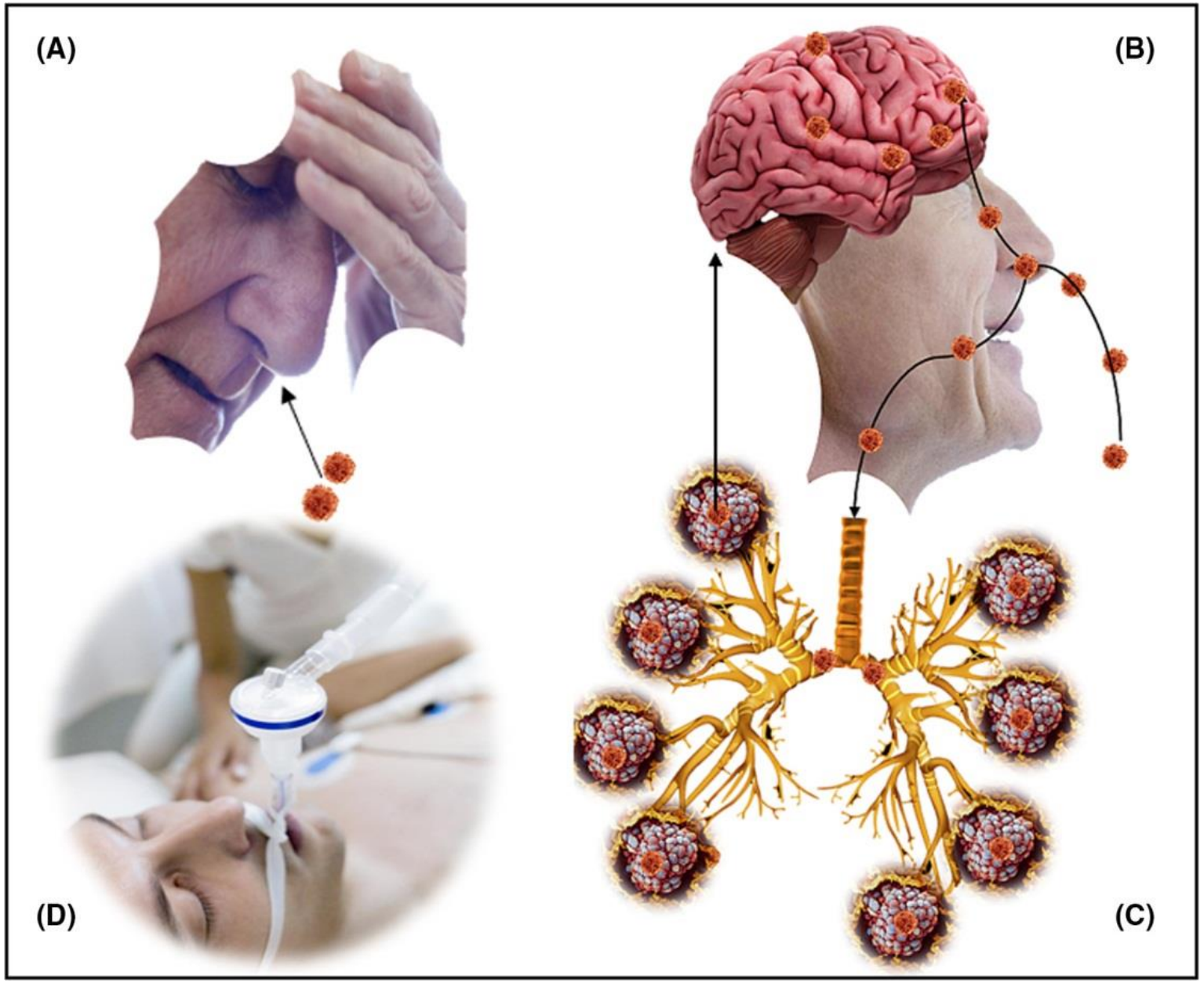


Introduction And Background

- Coronavirus disease 2019 (COVID-19) has been declared a pandemic on the 11th of March, 2020 by the World Health Organization.
- The epicenter of this pandemic has shifted in quick succession from China to Europe and United States of America in a matter of weeks.



Neurological manifestations in COVID-19 caused by SARS-CoV-2



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- COVID-19 affects different people in different ways. Most infected people will develop mild to moderate illness and recover without hospitalization.
- Most common symptoms:
- fever
- dry cough
- tiredness

- Less common symptoms:
- aches and pains
- sore throat
- diarrhea
- Conjunctivitis (pink eye)
- headache
- loss of taste or smell
- a rash on skin, or discoloration of fingers or toes
- Serious symptoms:
- difficulty breathing or shortness of breath
- chest pain
- loss of speech or movement

- On March 4, 2020, Beijing Ditan Hospital reported for the first time a case of viral encephalitis caused by a novel coronavirus (CoV) attacking the central nervous system (CNS).

- The researchers confirmed the presence of SARS-CoV-2 in the cerebrospinal fluid by genome sequencing.

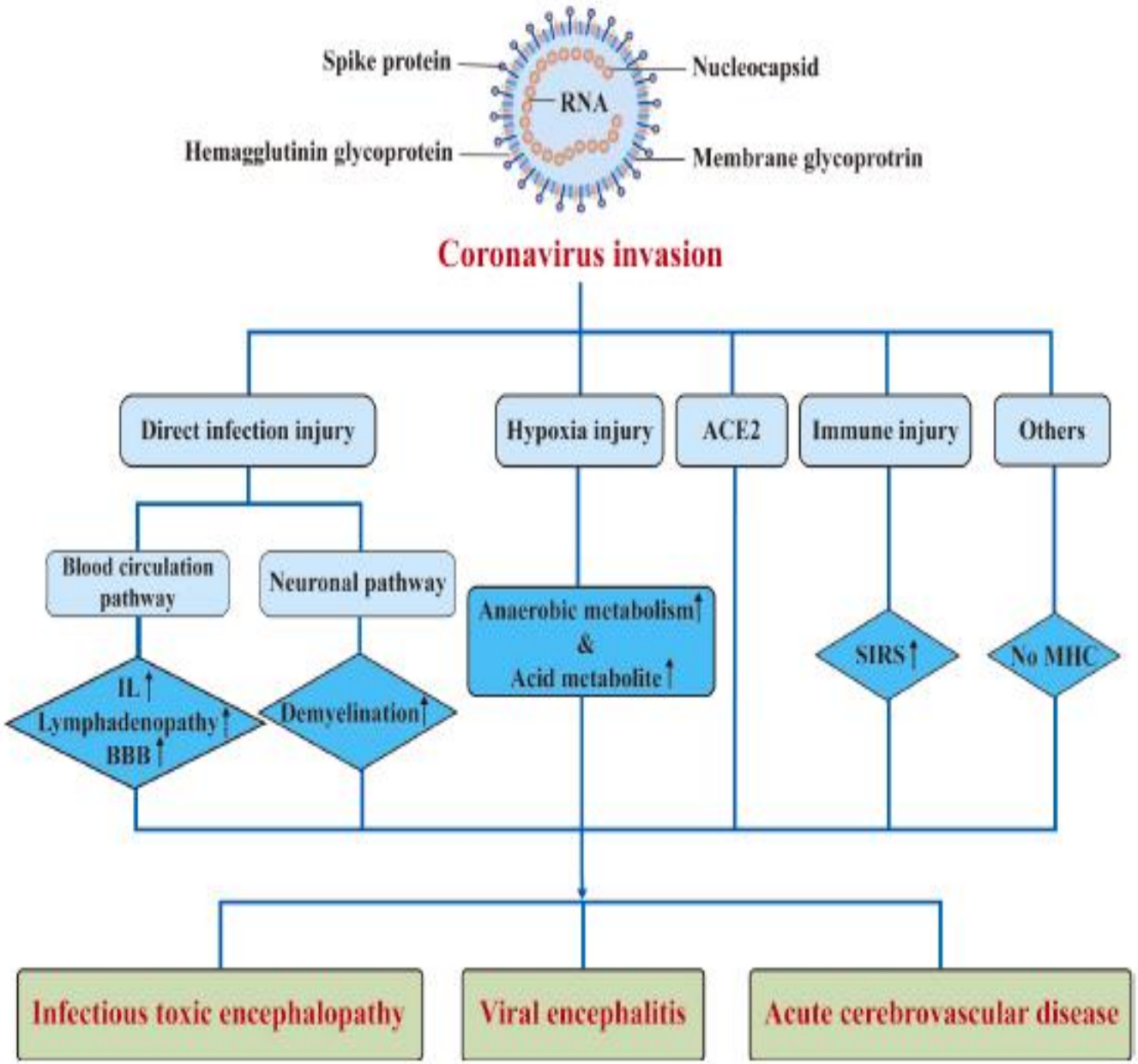
- Neurologic complications in patients with COVID-19 are common and occur in approximately half of hospitalized patients.
- headache,
- dizziness,
- myalgia,
- alteration of consciousness,
- disorders of smell and taste,
- weakness,
- strokes,
- and seizures.

- Neurological involvement in coronavirus disease 2019 (COVID- 19) corresponds to three situations:
- (a) neurological manifestations of viral infection
- (b) Post - infective neurological complications
- (c) infection in patients with neurological comorbidity.
- Neurologically ill patients who require immunosuppressive agents.
- multiple sclerosis
- myasthenia gravis

Mechanisms of CoV infections on the nervous system damage

- **Blood circulation pathway**: hematogenous spread .
- **Direct viral invasion:** of the brain leading to clinical encephalitis has been suspected after the treatment team of Beijing Ditan Hospital confirmed the presence of SARS-CoV-2 in the cerebrospinal fluid (CSF) of patients with COVID-19 by genome sequencing .
- **Neuronal pathway :**Viruses can migrate by infecting sensory or motor nerve endings, olfactory bulb in the nasal cavity

pathophysiology



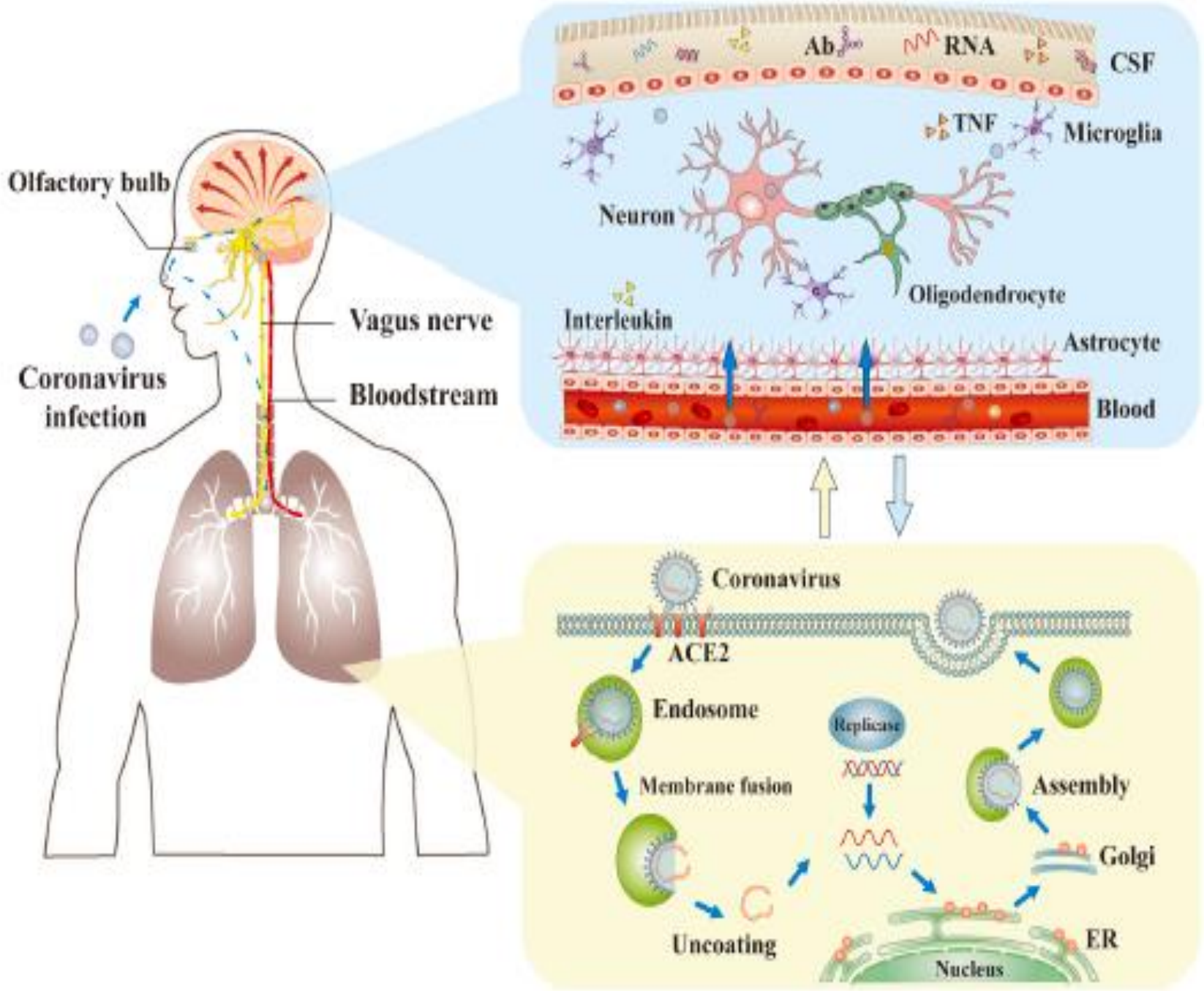

Olfactory bulb
Vagus nerve
Coronavirus infection
Bloodstream
Ab
RNA
CSF
TNF
Microglia
Neuron
Oligodendrocyte
Interleukin
Astrocyte
Blood
Coronavirus
ACE2
Endosome
Membrane fusion
Uncoating
Replicase
Assembly
Golgi
ER
Nucleus

Figure 2. Transsynaptic Viral Spread

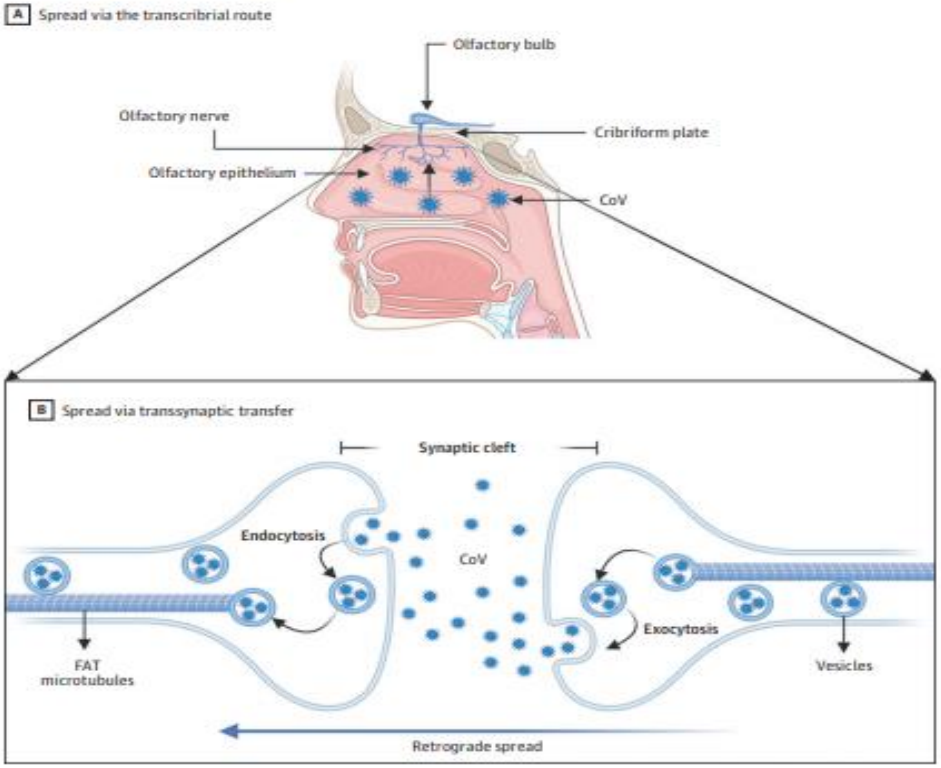


Figure 3. Mechanisms of Spread Across the Blood-Brain Barrier

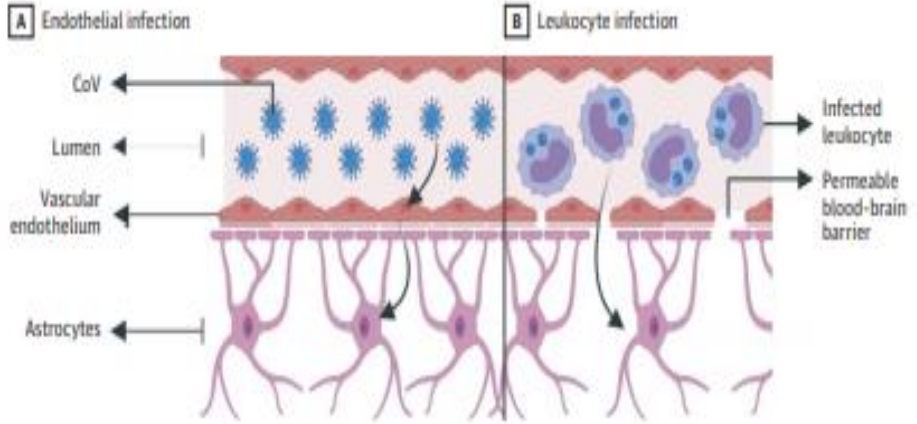


Table Acute neurologic complications of coronavirus infections

Viral meningitis
Anosmia
Encephalitis
Postinfectious acute disseminated encephalomyelitis
Postinfectious brainstem encephalitis
Guillain-Barré syndrome
Myositis
Acute necrotizing hemorrhagic encephalopathy

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SPECIAL EDITORIAL

Neurologic complications of coronavirus infections

Avindra Nath, MD

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Correspondence
Dr. Nath
natha@ninds.nih.gov

Neurological manifestations can be subdivided into the :

- **Central nervous system :**

- headache, dizziness, alteration of the sensorium, ataxia, encephalitis, stroke, and seizures

- **Peripheral nervous system :**

- skeletal muscle injury
- peripheral nerve involvement including hyposmia and hypogeusia

- **Post-infective neurological complications :**

demyelinating conditions (central , peripheral)

Mechanism of neuro-invasion

- **Hypoxia injury :** respiratory insufficiency, and hypoxia
- **Immune injury :**
  - Systemic inflammatory response syndrome (SIRS) ⟹ multiple organs failure (MOF)
  - Cytokine storm, interleukin (IL)-6
- **Coagulopathy and vascular endothelial dysfunction** have been proposed as complications of Covid-19.
- **Angiotensin-converting enzyme 2 (ACE 2)**

Angiotensin-converting enzyme 2

- Angiotensin-converting enzyme 2 (ACE2) is an enzyme attached to the outer surface (cell membranes) of cells in the lungs, arteries, heart, kidney, and intestines.
- ACE2 lowers blood pressure by catalysing the hydrolysis of angiotensin II (a vasoconstrictor peptide) into angiotensin (a vasodilator).
- ACE2 also serves as the entry point into cells for some coronaviruses.

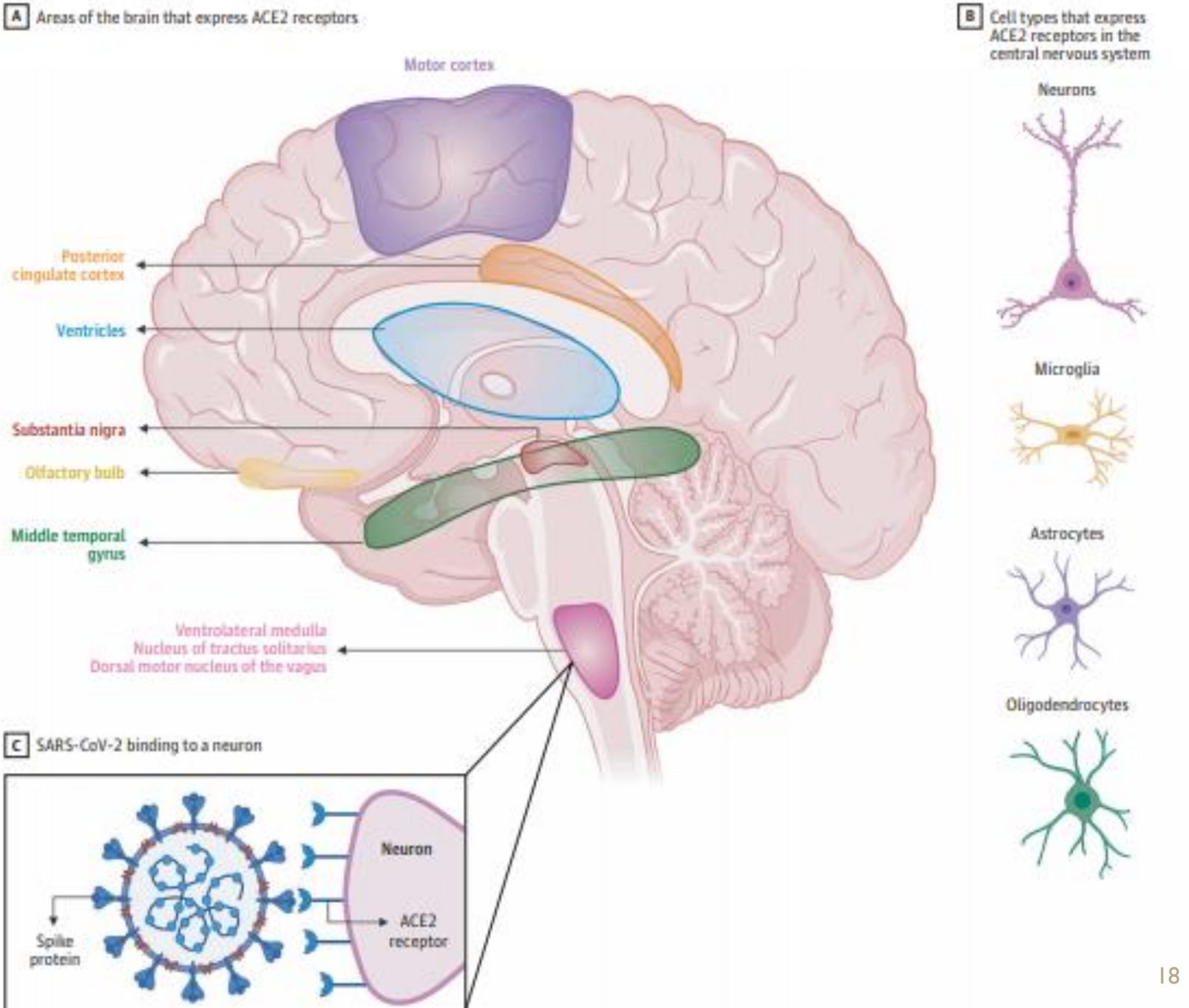
Angiotensin-Converting Enzyme-2 (ACE-2)

- The affinity of the viral particle towards angiotensin-converting enzyme-2 (ACE- 2),

  a cardio-cerebral vascular protection factor.

- It has been postulated that the viral attachment to the ACE-2 at the level of the blood-brain barrier may jeopardize the protective mechanism surrounding the encephalon, giving way to viral encephalitis.

Figure 1. Angiotensin-Converting Enzyme 2 (ACE2) Expression in the Brain



- Spinal cord membranes expressing ACE-2 can culminate into myelitis-like features following SARS-CoV-2 infection.
- Concern has also been raised that the viral particles binding to ACE-2 in cerebral blood vessels may actually raise the luminal pressure of those vessels leading to intracerebral hemorrhage .

Central nervous system :

- Headache
- Cerebro Vascular Events (CVE)
- Impaired consciousness
- Seizure
- Post-infective neurological complications

Central nervous system :

Headache : incidence : 6 to 13% in COVID-19 cases

- symptom of viral infection
- viral meningitis
- encephalitis

may reveal itself subsequently in the form of drowsiness and seizures.

Central nervous system :

- Cerebro Vascular Events (CVE) : case series study from Wuhan, China : 5.7%
- Ischemic stroke > ICH , CVT

Accelerated thrombosis :

viral infection may have given way to an inflammatory storm that ultimately culminated in accelerated thrombosis.

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

COVID-19 CASES

To rapidly communicate information on the global clinical effort against Covid-19, the Journal has initiated a series of case reports that offer important teaching points or novel findings. The case reports should be viewed as observations rather than as recommendations for evaluation or treatment. In the interest of timeliness, these reports are evaluated by in-house editors, with peer review reserved for key points as needed.

Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young

- Five cases of large-vessel stroke in patients younger than 50 years of age who presented to health system in New York City.
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was diagnosed in all five patients.

Central nervous system :

Impaired consciousness :

- Reported in 7.5% hospitalized patients of COVID-19.
- In severely affected patients are more likely to present impaired consciousness

- viral encephalitis,
- metabolic perturbation,
- infectious toxic encephalopathy,
- seizures with post-ictal confusion
- stroke

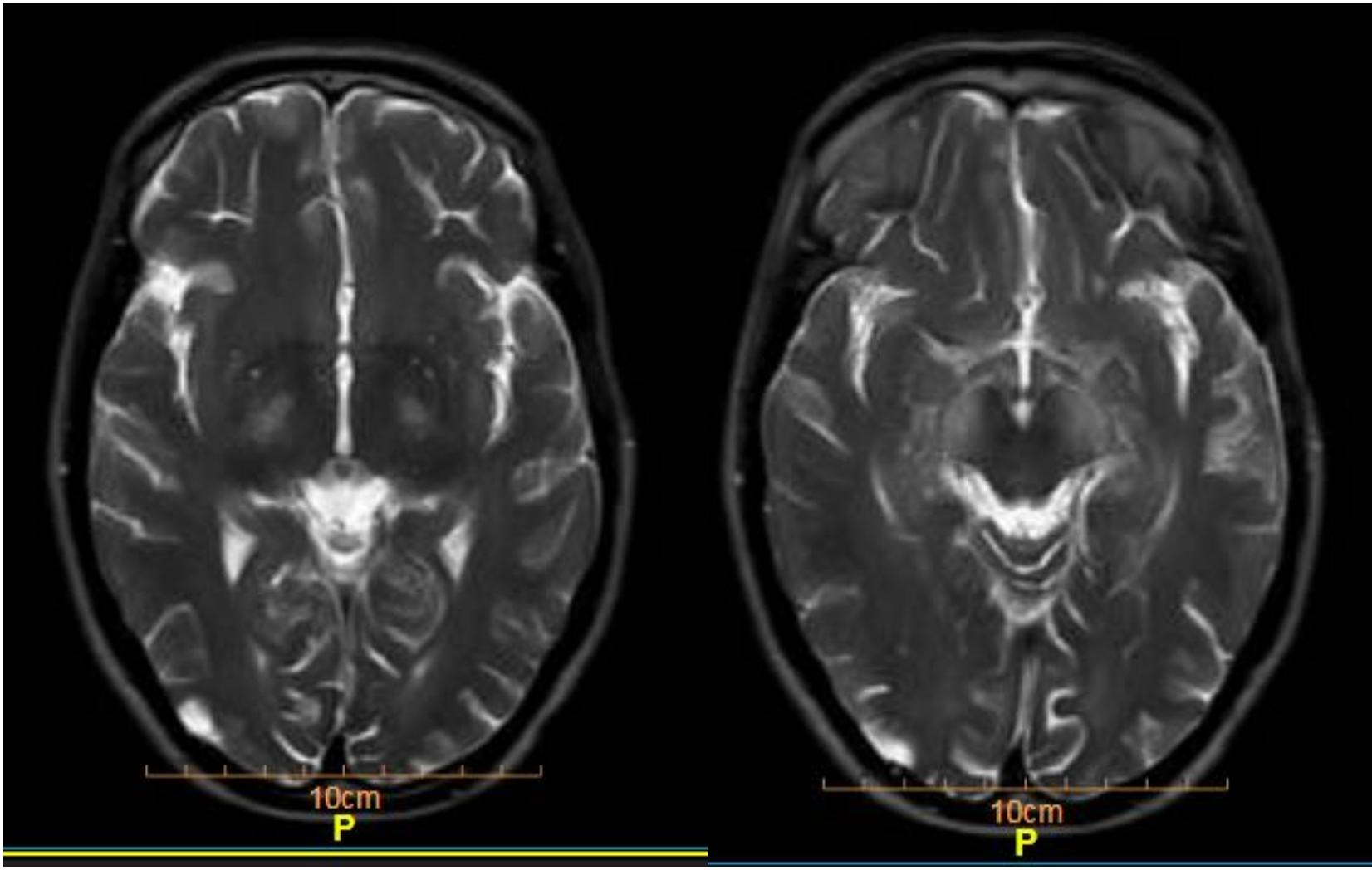
Central nervous system :

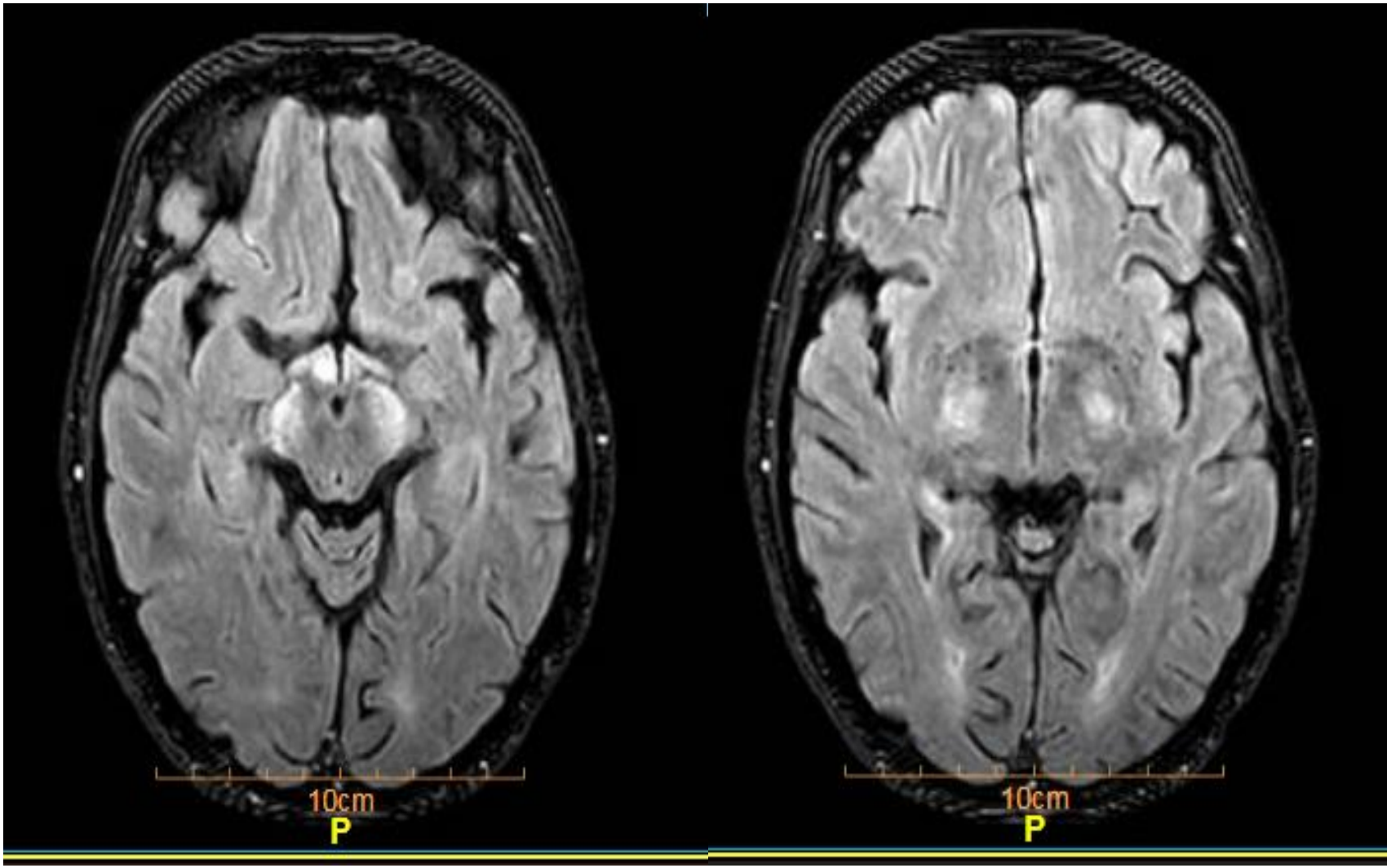
- **Seizure :**
- A case report of a patient with no history of epilepsy who had multiple apparent tonic-clonic seizures in the setting of COVID-19 may represent an unmasked seizure disorder or the direct effect of COVID-19 in the CNS, but further study in these cases are needed.

Post-infective neurological complications

- CNS demyelinations
- Guillain-Barre syndrome
  - Early report of Guillain-Barre syndrome (GBS) is available from China
  - Report of five cases of GBS collected from three hospitals of northern Italy among 100 to 1200 cases of SARS-CoV-2 infection over three weeks .
- Acute myelitis :
  - Another report from China describes a case of acute myelitis, possibly affecting the cervical spinal cord

CNS demyelination

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Case report

Guillain Barre syndrome associated with COVID-19 infection: A case report

Zahra Sedaghat [a], Narges Karimi [b,*]

[a] Neurology Resident, Department of Neurology, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[b] Toxoplasmosis Research Center, Immunogenetics Research Center, Clinical Research Development Unit of Ibn Ali Sina Hospital, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

CLINICAL/SCIENTIFIC NOTES | OPEN ACCESS

Guillain-Barré syndrome related to COVID-19 infection

Paola Alberti, MD, PhD,* Simone Beretta, MD, PhD,* Marco Piatti, MD, Aristotelis Karantzoulis, MD, Maria Luisa Piatti, MD, Patrizia Santoro, MD, Martina Viganò, MD, Ginevra Giovannelli, MD, Fiammetta Pirro, MD, Danilo Antonio Montisano, MD, Ildebrando Appollonio, MD, and Carlo Ferrarese, MD, PhD

Correspondence
Dr. Alberti
paola.alberti@unimib.it

Neurol Neuroimmunol Neuroinflamm 2020;7:e741. doi:10.1212/NXI.0000000000000741

Guillain-Barr´e syndrome (GBS) associated with COVID-19

- COVID-19 stimulates inflammatory cells and produces various inflammatory cytokines and as a result, it creates immune-mediated processes.
  - AMSAN
  - Demyelinating type
  - Miller fisher syndrome

Patients with neurological co-morbidity

1- Multiple sclerosis :

- Prototypical with long term immunosuppression.
- A recent article on this topic recommends that the benefits of continuing immunotherapy in patients with multiple sclerosis (MS) and related disorders may outweigh the risks of medication withdrawal in the apprehension of COVID-19.

- This is particularly because most infections, as in the general population, are anticipated to be mild and self-limiting.
- However, the authors emphasize the need for individualized decision making in such circumstances because one size may not fit all, and some of the patients may land up in severe infection leading to discontinuation of therapy.

2- Neuromuscular disorders

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INVITED ARTICLE

COVID-19 and neuromuscular disorders

Amanda C. Guidon, MD, and Anthony A. Amato, MD

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Correspondence
Dr. Guidon
aguidon@partners.org
or Dr. Amato
aamato@bwh.harvard.edu

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Clinical short communication

Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic

International MG/COVID-19 Working Group[1], Saiju Jacob[a,*,2], Srikanth Muppidi[b,*,2], Amanda Guidon[c], Jeffrey Guptill[d], Michael Hehir[e], James F. Howard Jr[f], Isabel Illa[g], Renato Mantegazza[h], Hiroyuki Murai[i], Kimiaki Utsugisawa[j], John Vissing[k], Heinz Wiendl[l], Richard J. Nowak[m,*,2]

Risk of infection causing a new NMD

- Guillain-Barr´e syndrome (GBS) : There is reported cases of GBS in association with COVID-19

  however, direct causality is uncertain.
- Myopathies : Coronavirus infections may be associated with myopathies.
- In recently published studies of COVID-19 in China, myalgia or fatigue affected 44%–70% of hospitalized patients and
- Increased creatine kinase (CK) was present in up to 33% of admitted patients.
- Very sick patients with coronavirus develop critical illness myopathy or polyneuropathy.

Risk of COVID-19 infection exacerbating known or unmasking previously unrecognized NMDs

- There are no data regarding magnitude of risk of exacerbation due to COVID-19 or prior coronaviruses for rare NMDs.
- Considerations for exacerbation in acquired and inherited disorders are primarily related to degree of baseline cardiac and respiratory dysfunction, bulbar weakness, underlying pathophysiology of disease, and related comorbid conditions.

Risks of immunosuppressant and immunomodulating therapies in patients with autoimmune NMDs

- Patients with NMDs who use immunosuppressive therapies (ISTs) are likely at increased risk of contracting COVID-19 or having a more severe course of the virus.
- Most outpatients without infection should continue to take their medications, with instructions to call their neurologist and temporarily hold the medication if they develop symptoms of infection.

Management of patients with NMD who develop COVID-19

- At this time, there are no neuromuscular-specific recommendations for patients who contract COVID-19 and additional outcome data are needed.
- Monitoring moderate to high risk patients with NMDs closely for the possibility of more rapid decline in respiratory function or for worsening of their underlying neuromuscular disease is recommended.
- Patients with NMD already on corticosteroids may require stress doses.

Patients on existing therapies for MG/LEMS

- MG/LEMS patients should continue their current treatment and are advised not to stop any existing medications, unless specifcally discussed and approved by their healthcare provider.

Patients on existing therapies for MG/LEMS

- Chloroquine and hydroxychloroquine :
- Have also been associated with new-onset or worsening MG and are typically used with caution in this patient group.
- Azithromycin :
- A macrolide antibiotic, is also being used with chloroquine or hydroxychloroquine for COVID-19. may cause worsening of MG.

Risks of treatments for COVID-19

- Chloroquine and Hydroxychloroquine :
- US Food and Drug Administration currently recommends exercising caution in using these drugs because of potential cardiotoxicity.
- Neurologic adverse effects include irritability, psychosis, peripheral neuropathy, and neuromyopathy.
- Hydroxychloroquine exacerbate symptoms in myasthenia gravis and contraindicated for patients with this disease.
- It also lowers the seizure threshold and interacts with several antiepileptic drugs, including lacosamide and lamotrigine.

Risks of treatments for COVID-19

- Tocilizumab :
- Tocilizumab is a monoclonal antibody to the IL-6 receptor that may attenuate cytokine release in patients with severe inflammatory disease.
- It has poor penetration into the CNS.
- Neurologic adverse effects include headache and dizziness, and there have been rare reports of multifocal cerebral thrombotic microangiopathy.

Risks of treatments for COVID-19

- Remdesivir :
- Remdesivir is a viral RNA–dependent RNA polymerase inhibitor.
- There is little noted about potential neurologic adverse effects, and clinical trials are ongoing.
- lopinavir/ritonavir :
- Toxic myopathy with rhabdomyolysis has been reported in several cases of lopinavir/ritonavir treatment in combination with a statin.

Thank you
For
your participation