CONCEPTS AND CONUNDRUMS OF COVID-19 NEUROLOGY

PRESENTER : DR.VAISHNAVI A

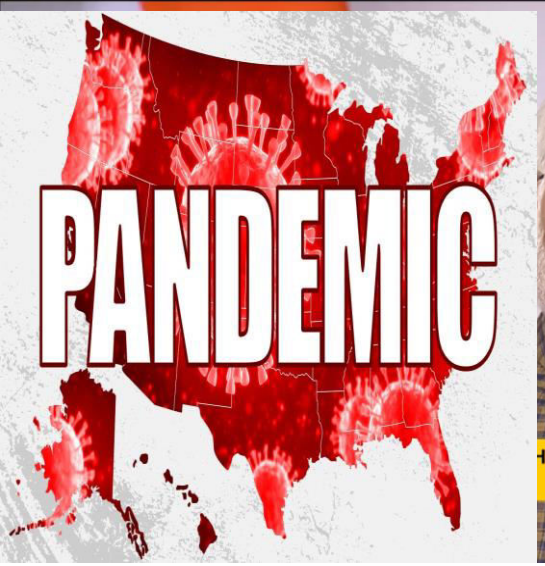
SENIOR RESIDENT

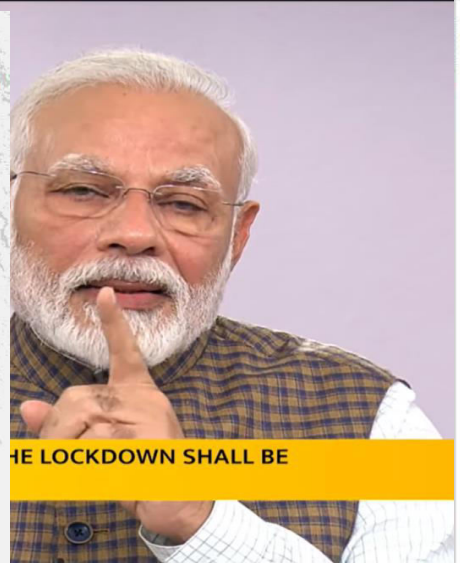
MODERATOR : DR. N.S.SAMPATH KUMAR

PROFESSOR & HOD

DEPARTMENT OF NEUROLOGY

NARAYANA MEDICAL COLLEGE





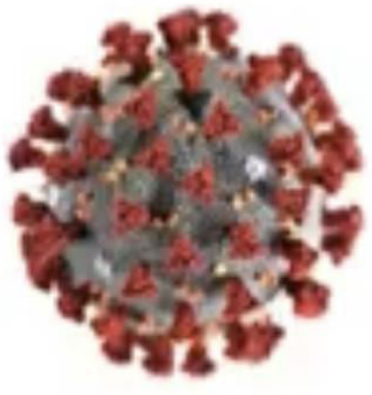
First reported from Wuhan , China as an Epidemic , and within few months developed into Pandemic , raging across the continents , disrupting human life as no other event in the living memory .

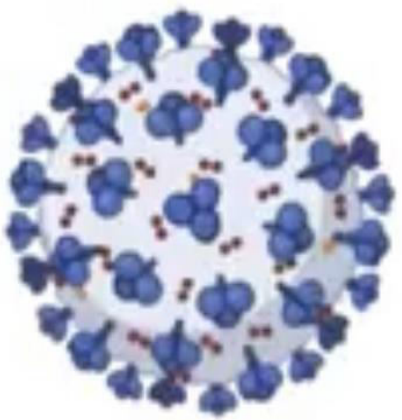
COVID-19 PANDEMIC has affected our lives , our economy and nearly every corner of globe .

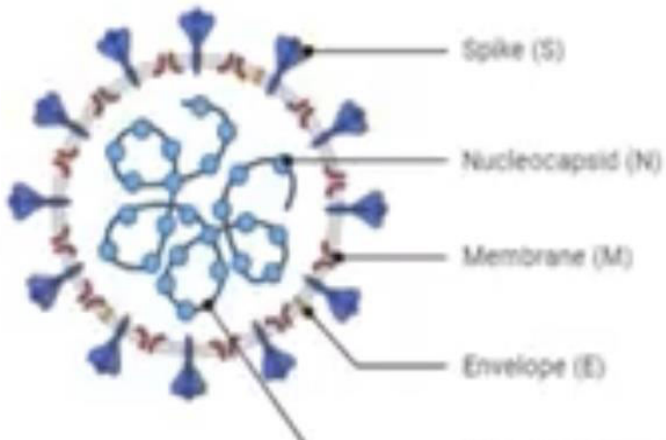
It is emerging as a greatest public health crisis in 21st century

INTRODUCTION

- ***SARS-CoV-2 is a betacoronavirus , enveloped , positive-sense , single-stranded RNA virus***
- ***Betacoronaviruses infect humans and mammals.***
- ***Bats and rodents acts as a natural reservoir .***
- ***In a phylogenetic analysis of 103 strains of SARS-CoV-2 from china , two different types of SARS-CoV-2 were identified-type L(70%) and type S(30%).***



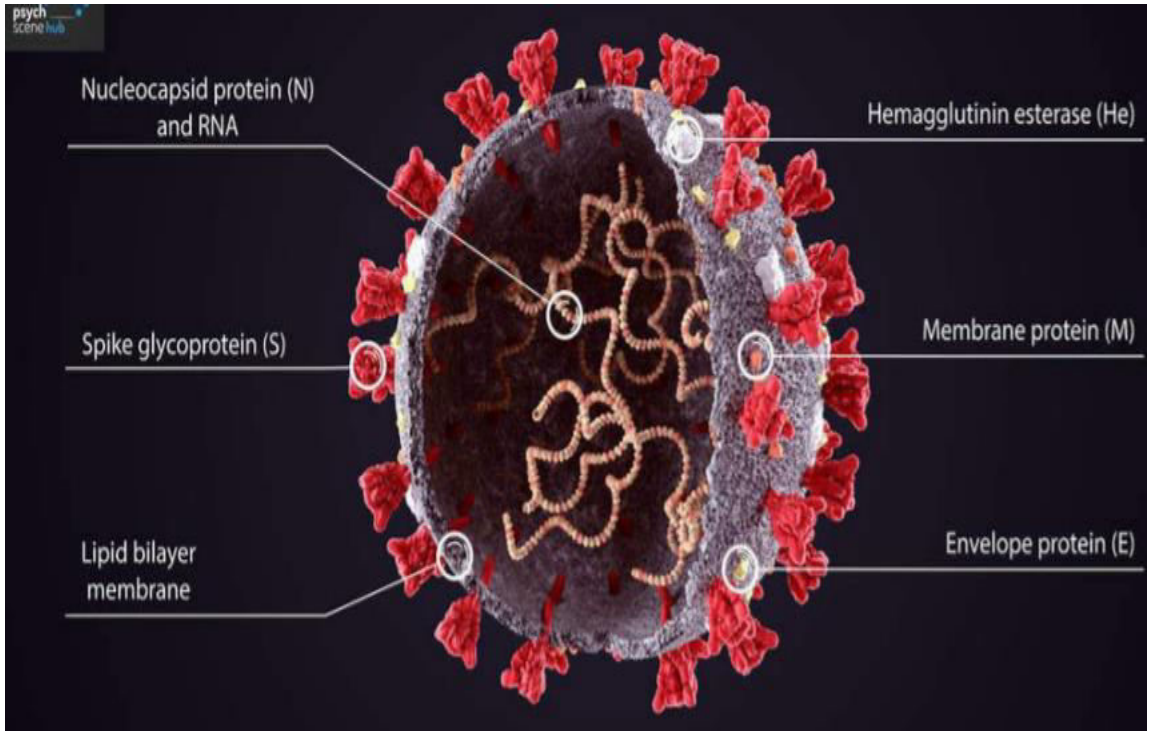




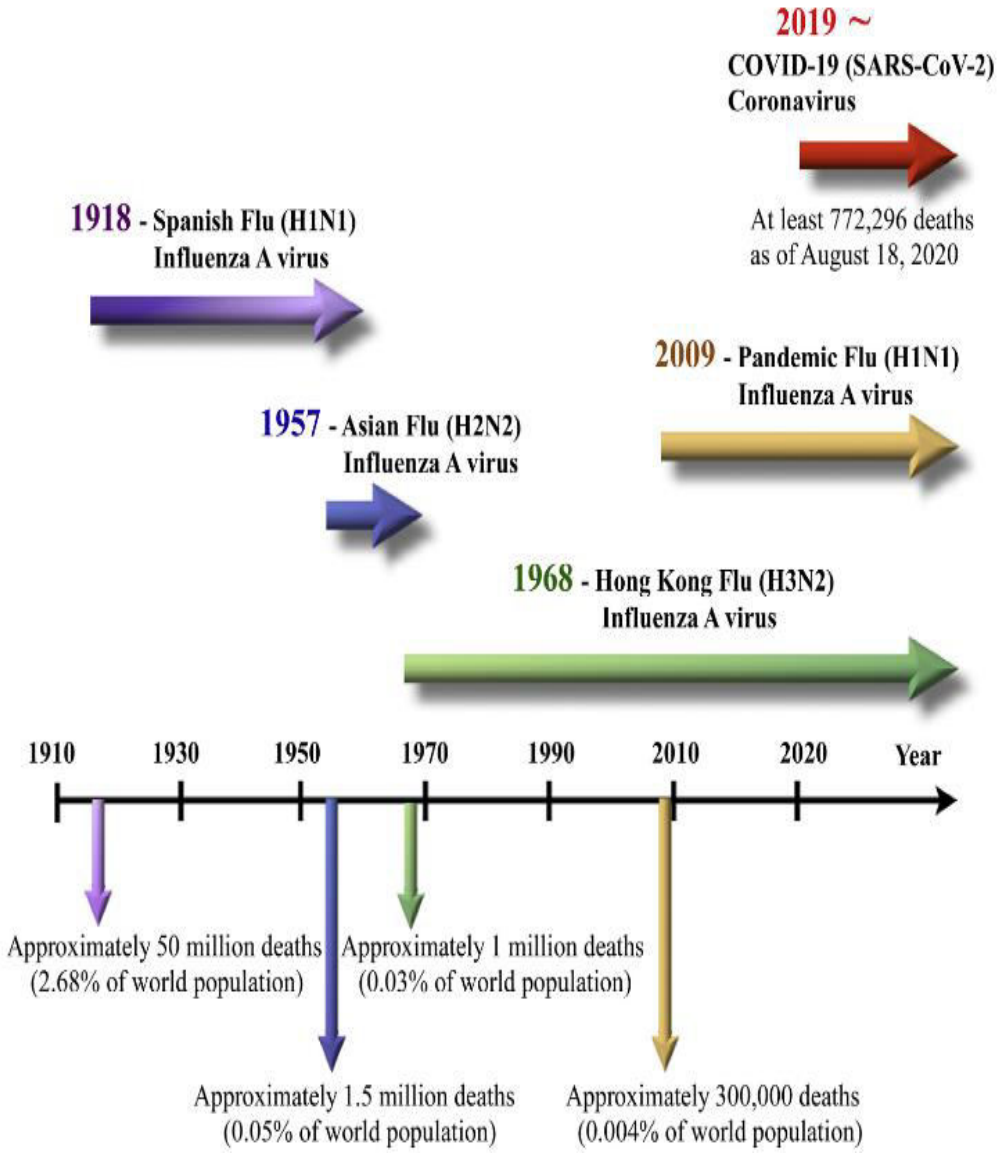
COVID-19 is the name of the Disease

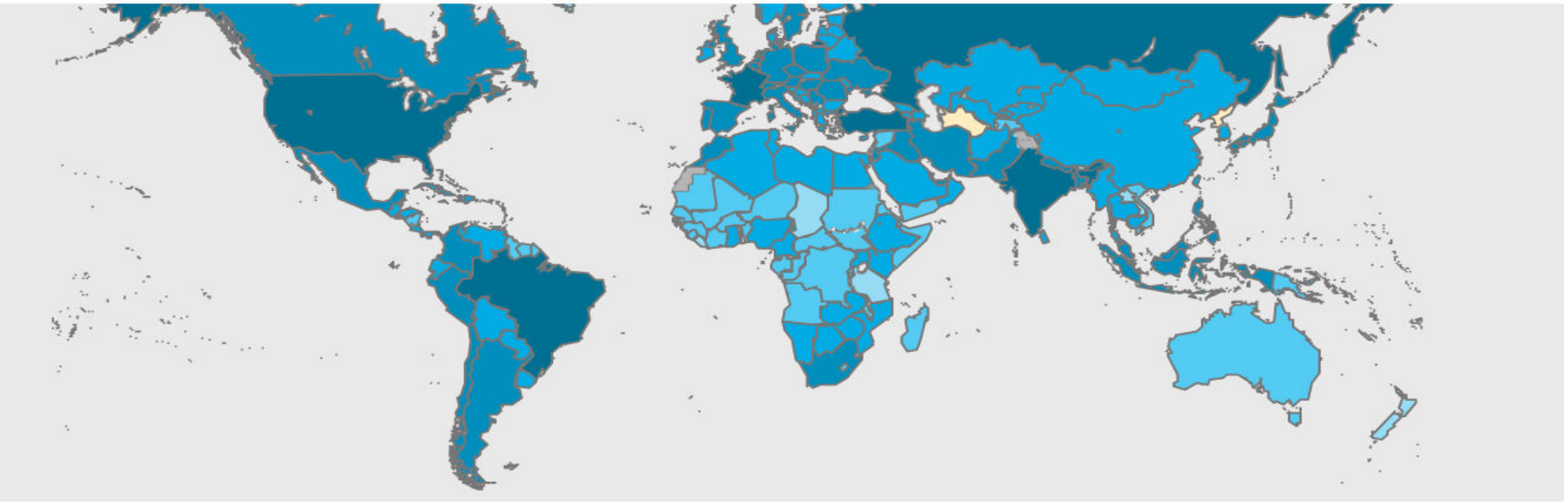
While

SARS-CoV2 is the name of the Virus



- *The current outbreak originated from Wuhan , China in December 2019 and subsequently spread world wide becoming a Global Health Concern .*
- *The Novel Human Corona Virus disease (COVID-19) has become the FIFTH documented Pandemic since the 1918 flu pandemic .*
- *WHO , has named this Infectious disease as COVID-19 on 12 February 2020.*
- *On March 11 , 2020 , WHO declared COVID-19 as a GLOBAL PANDEMIC.*
- *The virus is the seventh number of coronavirus family to infect Humans*





***Globally*, as of *6:27pm CEST, 6 July 2021*, there have been *183,934,913 confirmed cases* of COVID-19, including *3,985,022 deaths*, reported to WHO. As of *5 July 2021*, a total of *2,989,925,974 vaccine doses* have been administered.**

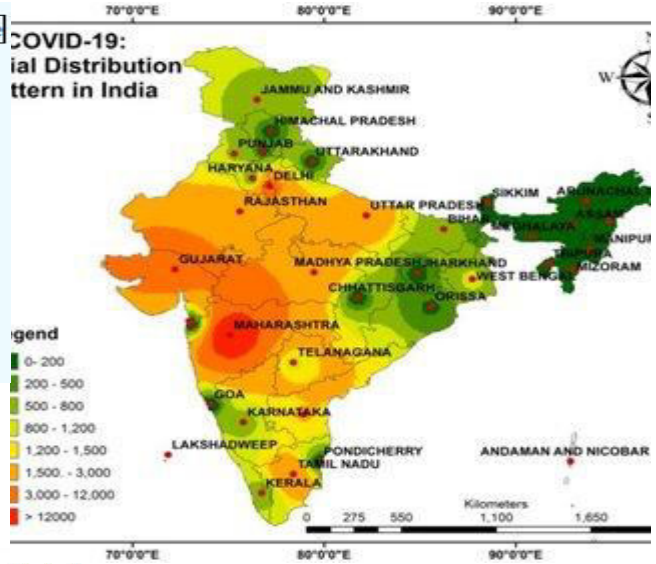
CASES ACROSS INDIA

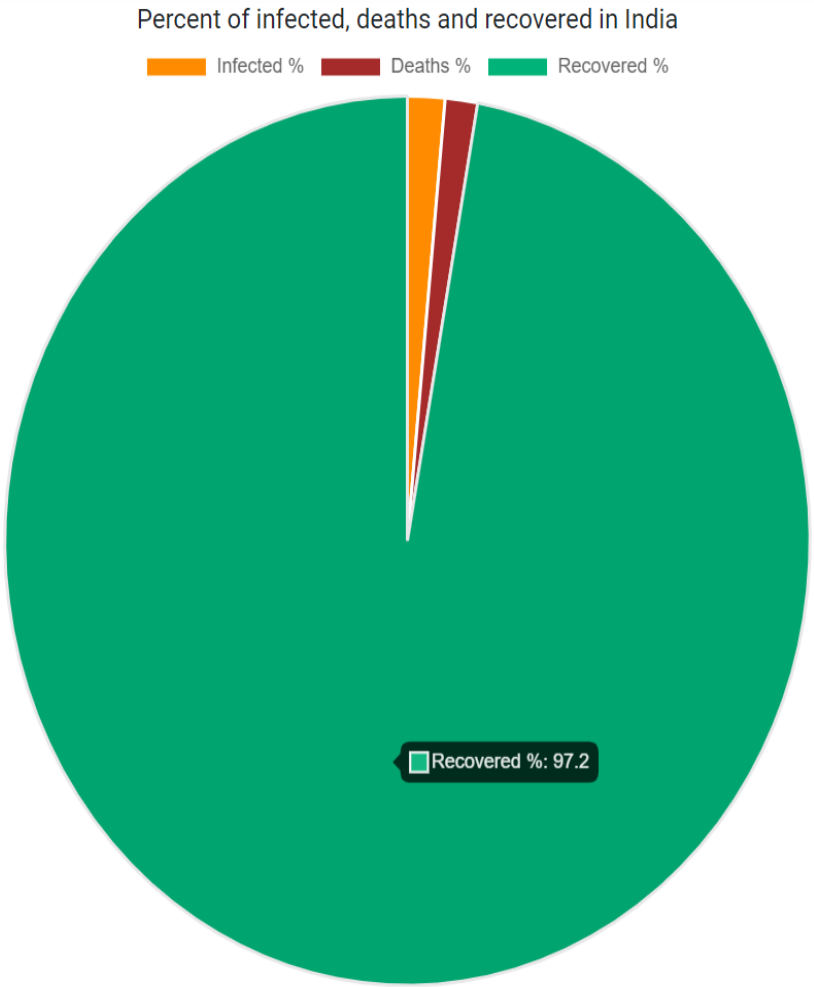
Statewise

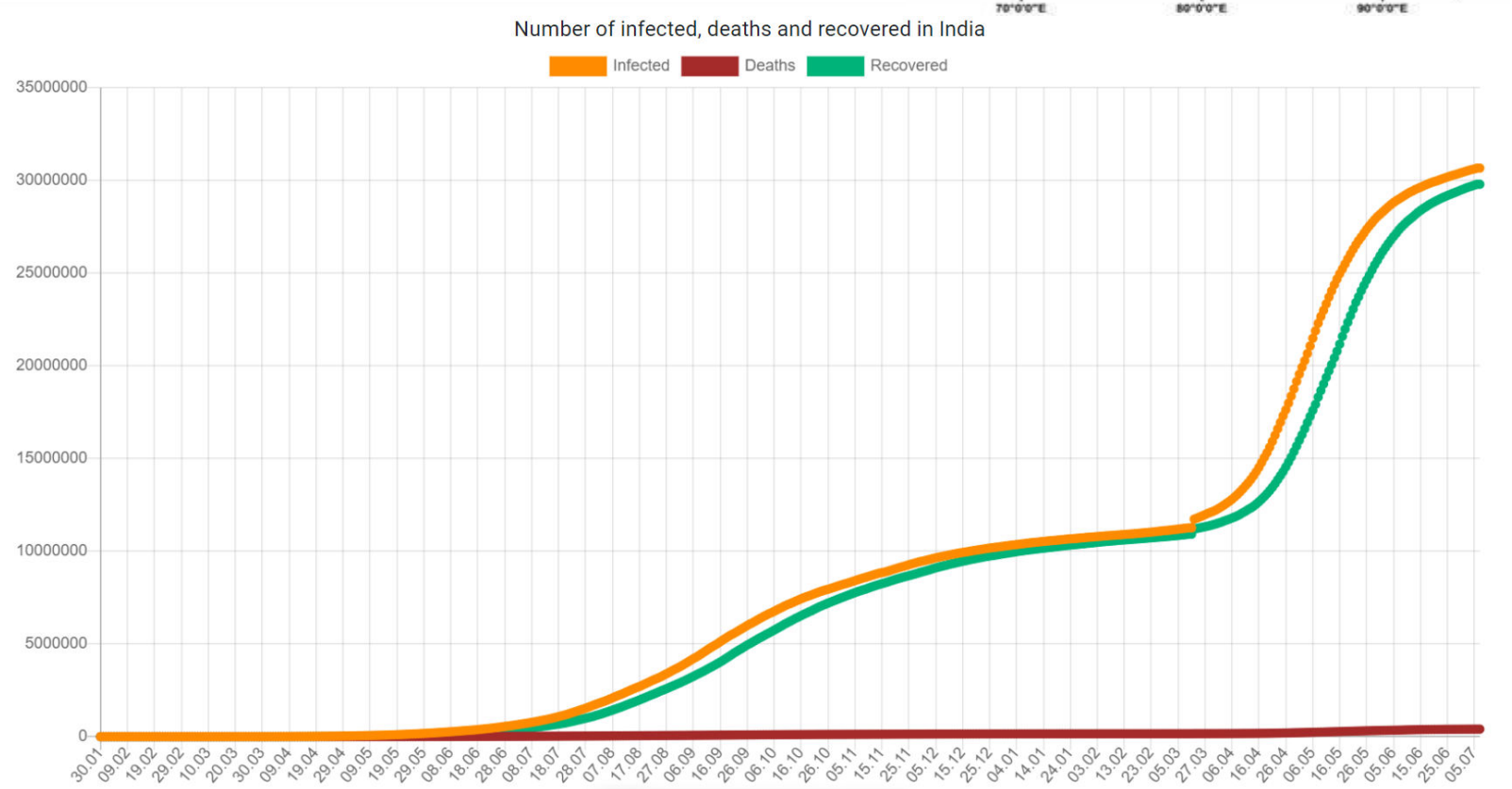
4,64,357 17,714 ↓

ACTIVE CASES (1.52%)

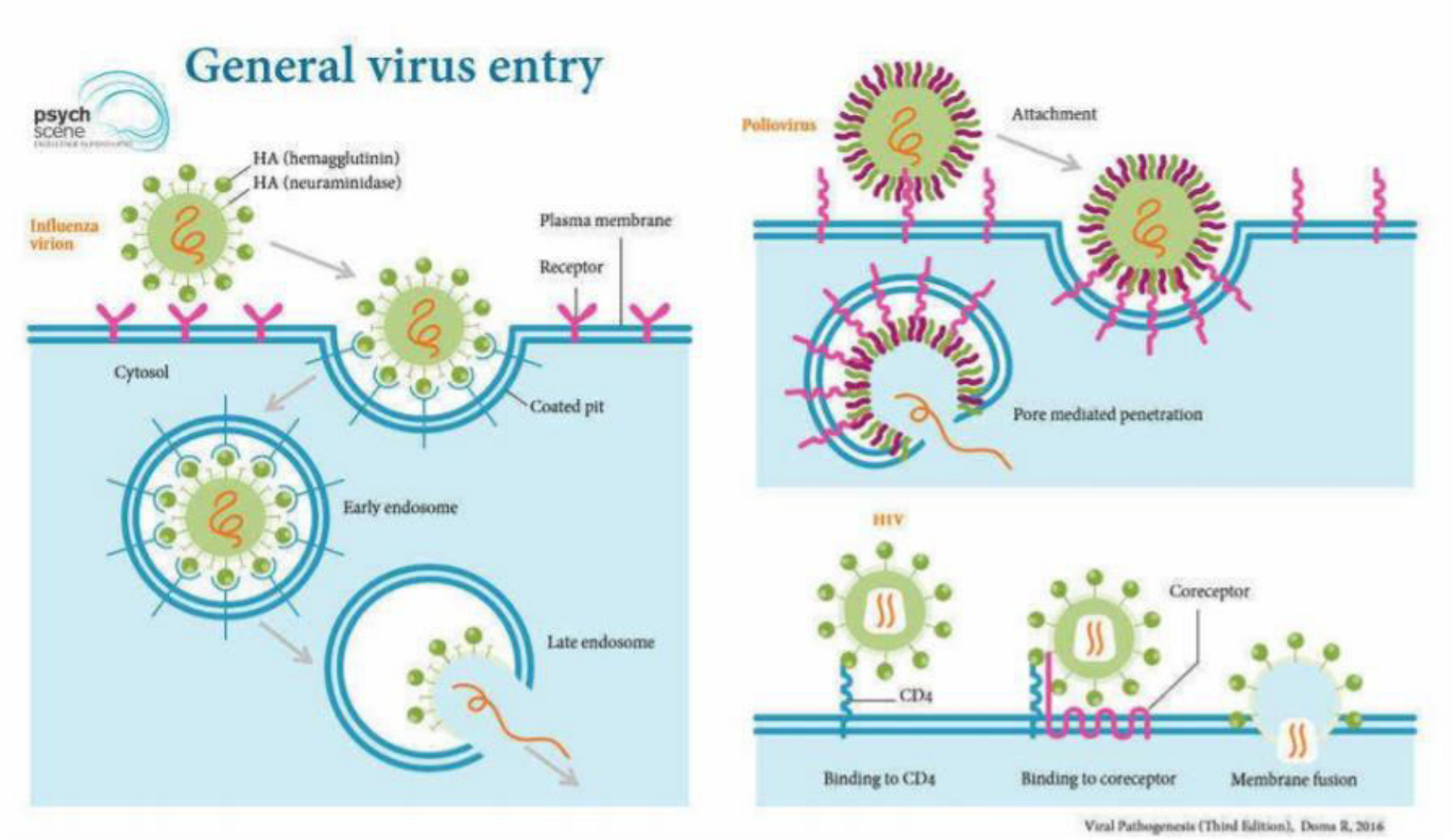
TOTAL CASES	DISCHARGED (97.17%)	DEATHS (1.32%)
3,06,19,932	2,97,52,294	4,03,281
34,703 ↑	51,864 ↑	553 ↑







MECHANISMS OF VIRUS ENTRY

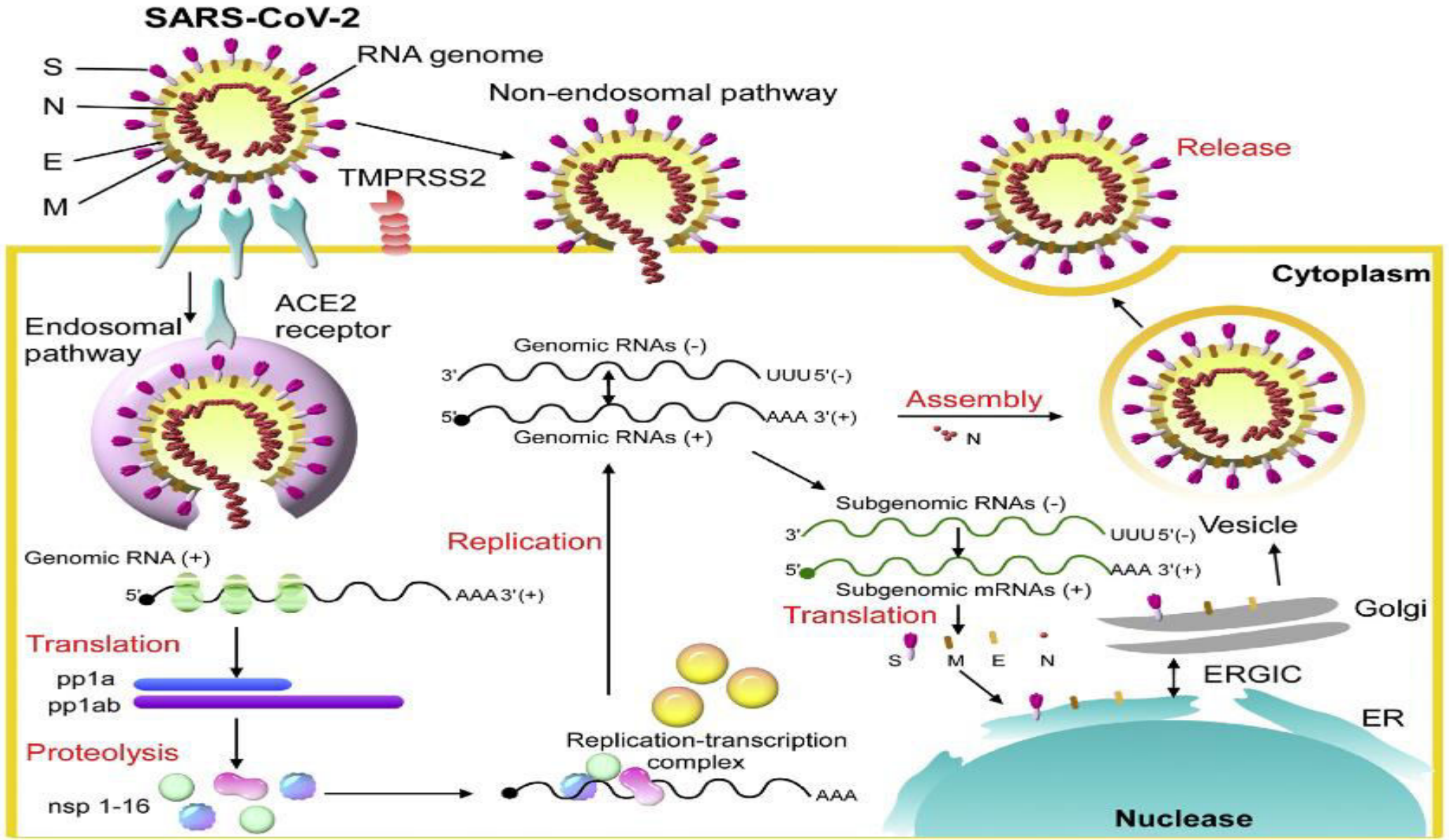


Viruses are Acellular particle which depend on the host cell machinery for replication .

Stages in a virus life cycle :

1. ***Attatchment***
2. ***Penetration***
3. ***Uncoating***
4. ***Replication***
5. ***Assembly***
6. ***Release***

SARS-CoV-2 Replication



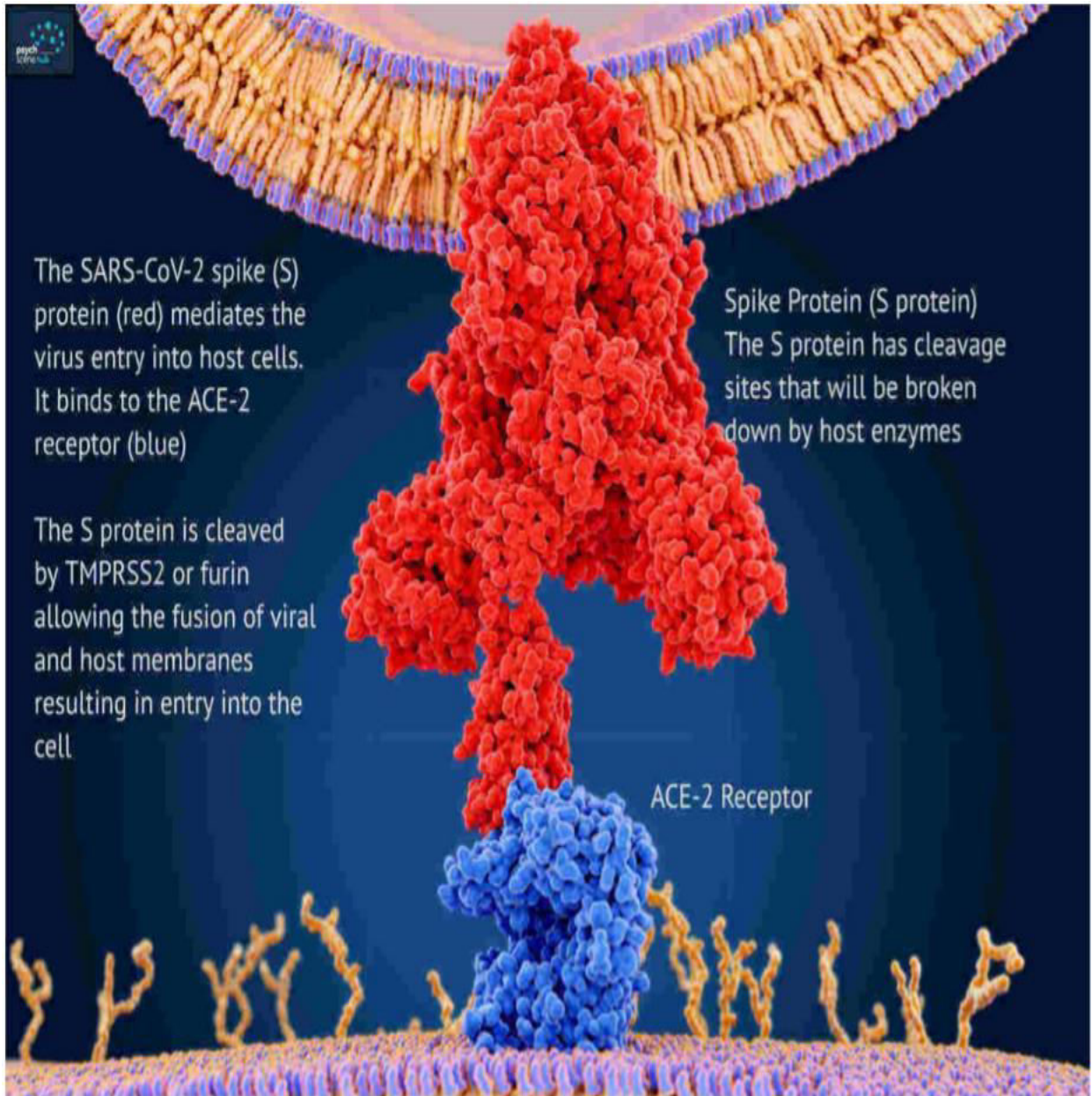
PATHOGENESIS OF SARS-CoV-2

***INFECTION POINTS** : Two specific nose cells (Goblet & Cilliated cells) expressing ACE-2 Receptors .*

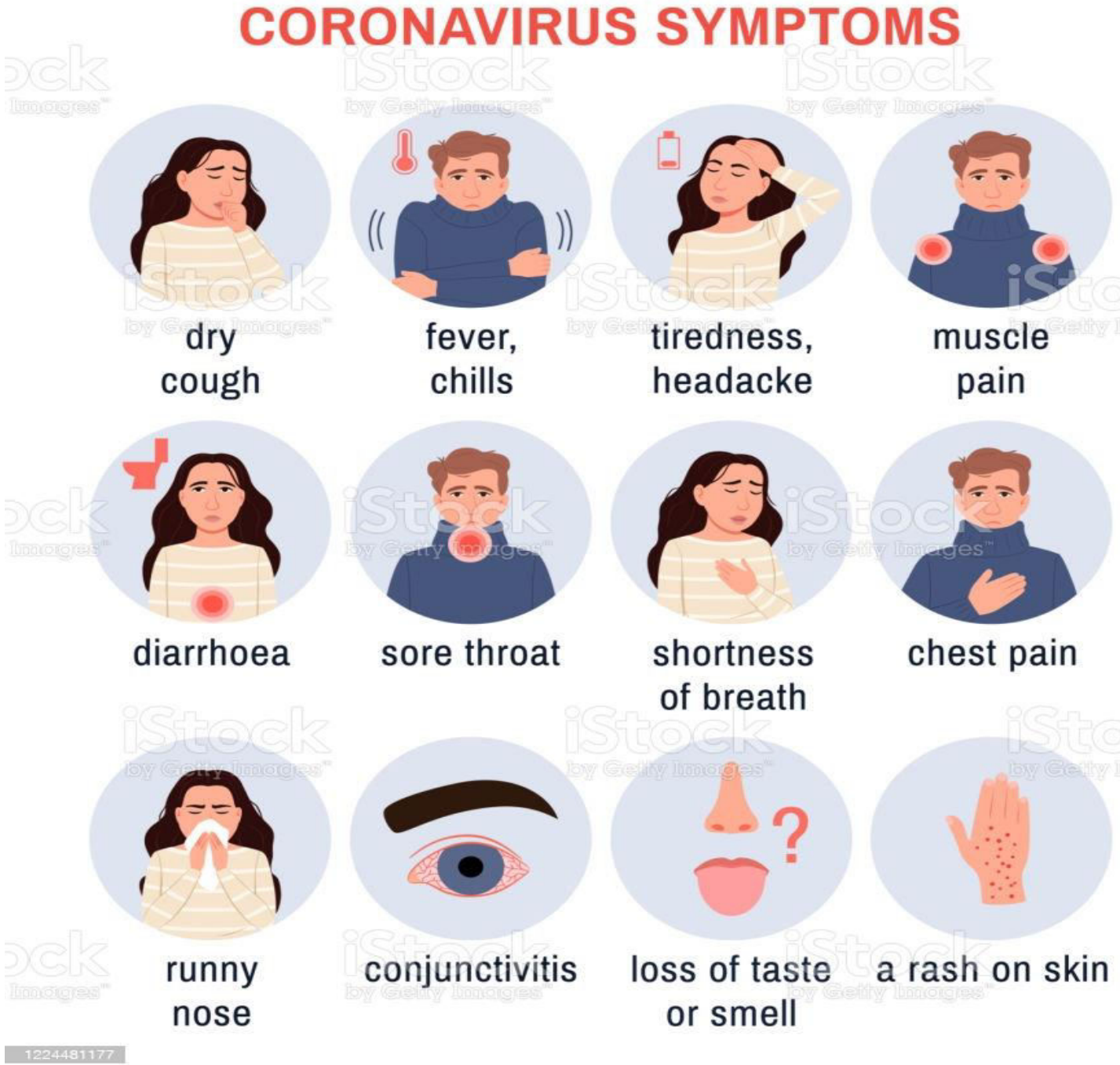
ACE-2 : ENTRY RECEPTOR
TMPRSS2 / FURIN : SPIKE PROTEIN PRIMING & FUSION PEPTIDES EXPOSURE

After FUSION , Virus enters the cells .

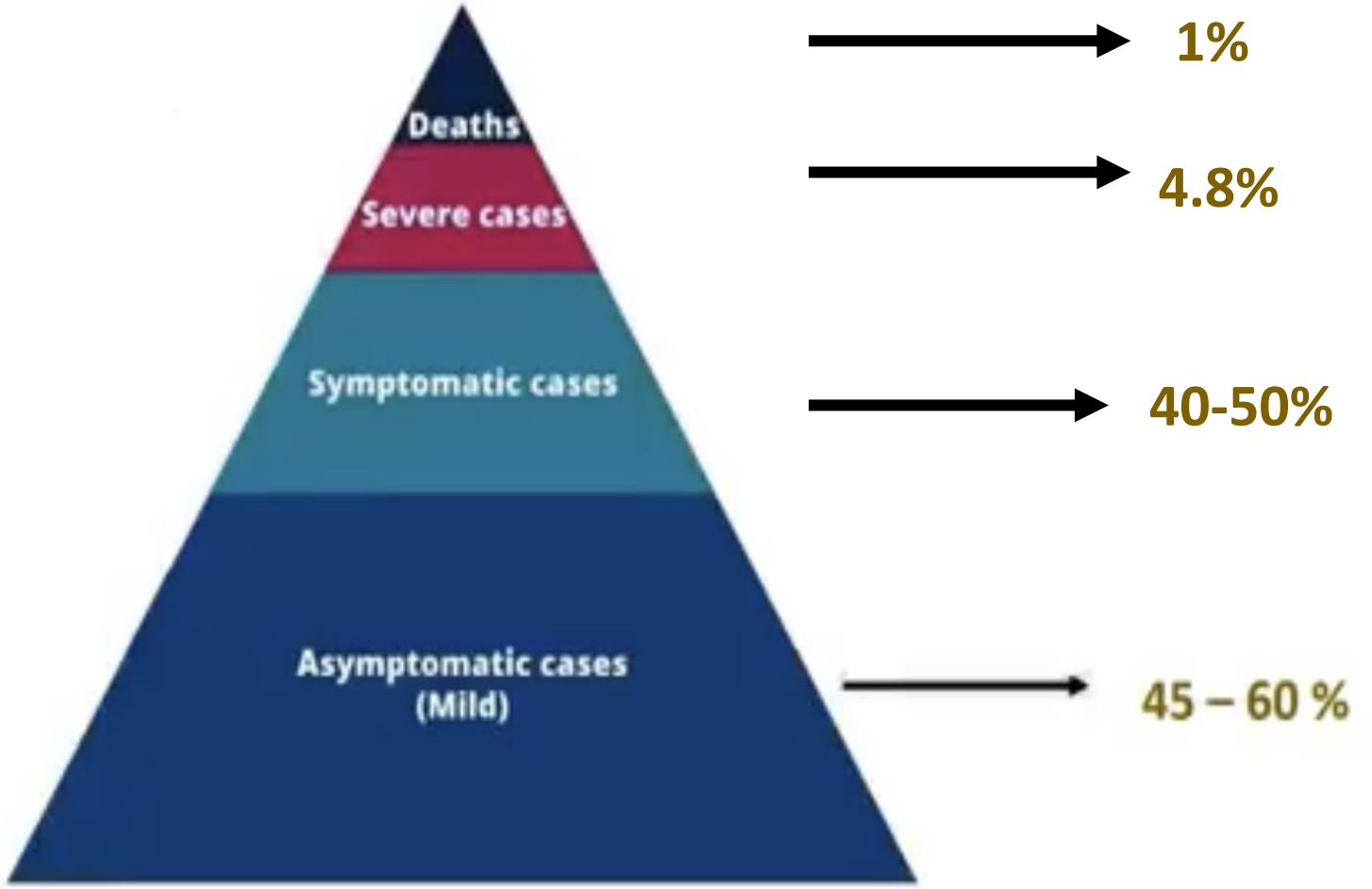
VIRAL REPLICATION :
Inside the host cell , foreign viral RNA ' HIJACKS ' the host cell machinery to produce RNA and proteins that produce new viral particles , which then exit the cell to infect new cells .



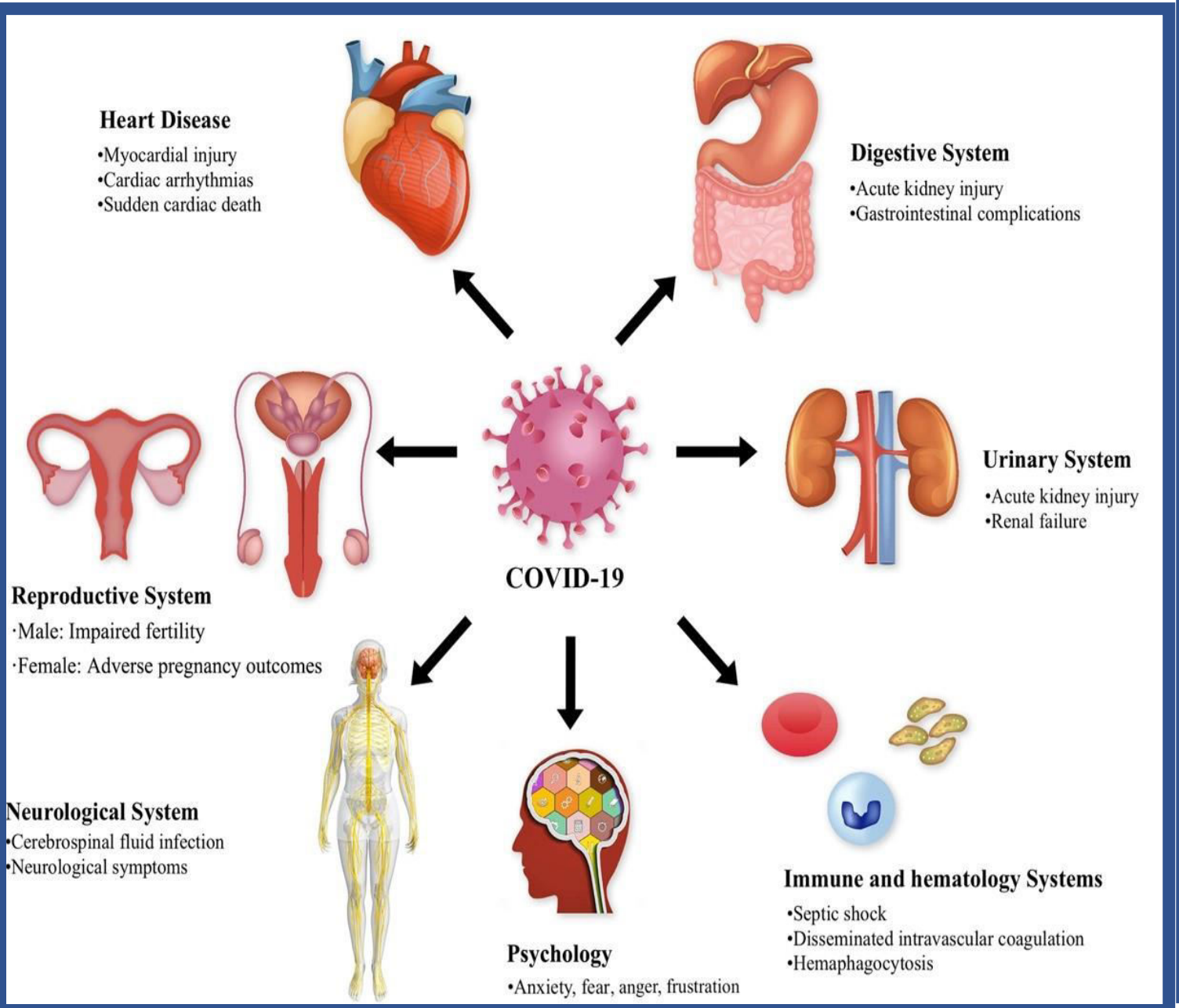
CLINICAL PRESENTATION

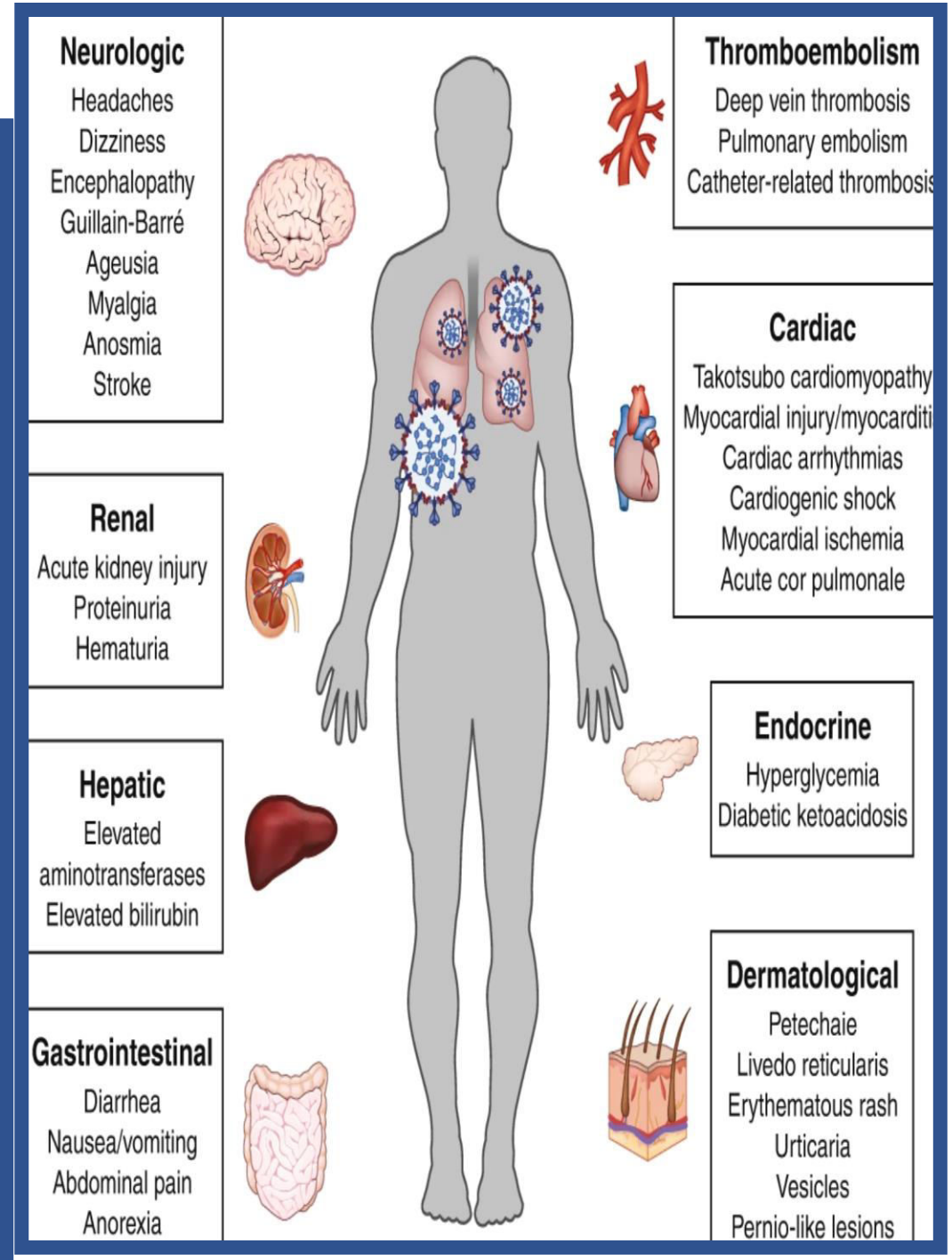


SPECTRUM OF COVID-19 CASES



EXTRAPULMONARY COMPLICATIONS OF COVID-19





EVIDENCE FOR CNS INVOLVEMENT

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INTERNATIONAL SOCIETY FOR INFECTIOUS DISEASES

Case Report

A first case of meningitis/encephalitis associated with SARS-Coronavirus-2

Takeshi Moriguchi[a,*], Norikazu Harii[b], Junko Goto[a], Daiki Harada[a], Hisanori Sugawara[a], Junichi Takamino[a], Masateru Ueno[a], Hiroki Sakata[a], Kengo Kondo[a], Natsuhiko Myose[a], Atsuhito Nakao[c], Masayuki Takeda[d], Hirotaka Haro[e], Osamu Inoue[f], Katsue Suzuki-Inoue[g], Kayo Kubokawa[h], Shinji Ogihara[i], Tomoyuki Sasaki[g], Hiroyuki Kinouchi[j], Hiroyuki Kojin[k], Masami Ito[k], Hiroshi Onishi[l], Tatsuya Shimizu[l], Yu Sasaki[l], Nobuyuki Enomoto[m], Hiroshi Ishihara[n], Shiomi Furuya[k], Tomoko Yamamoto[k], Shinji Shimada[o]

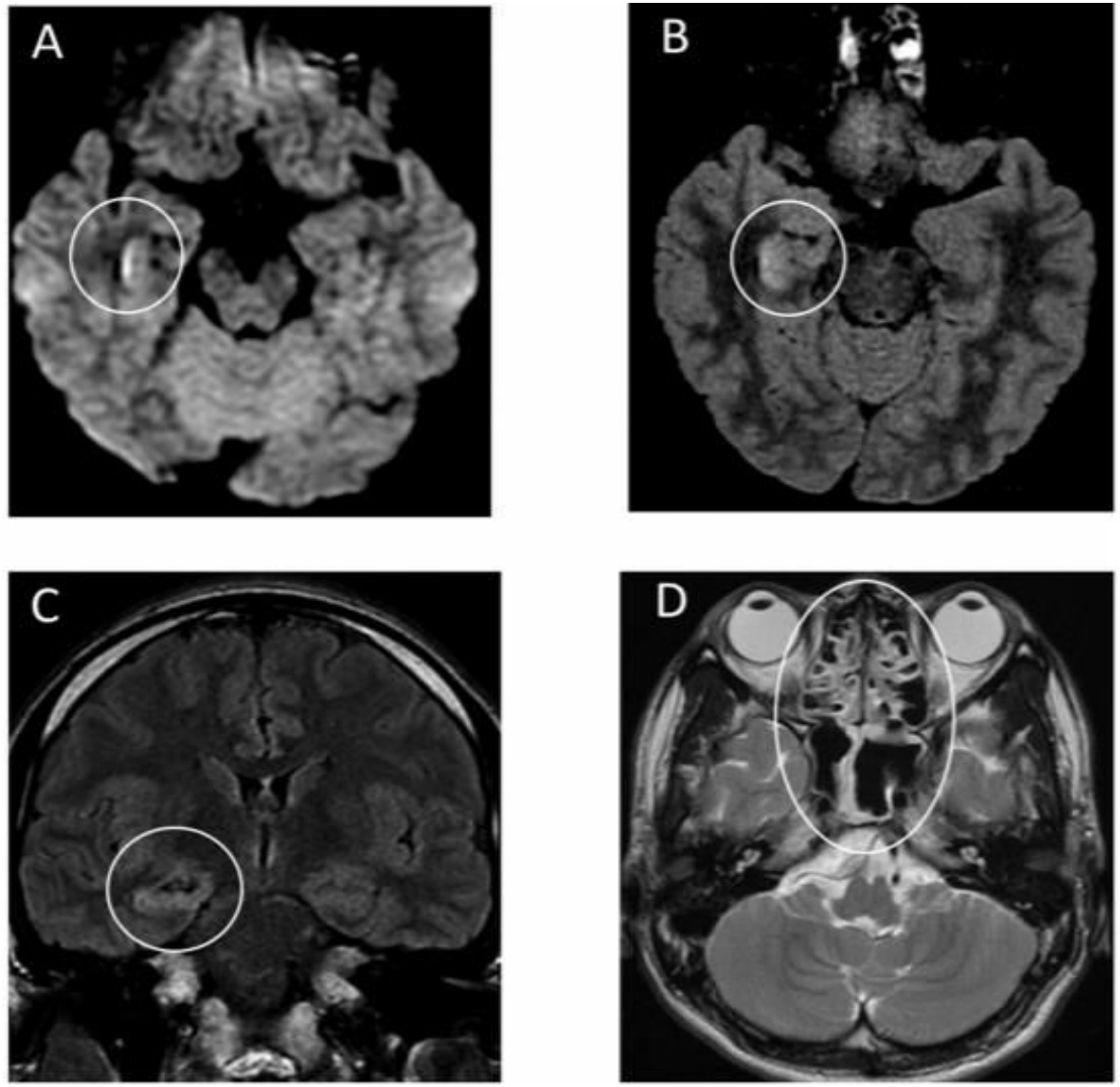


Figure 1. Brain MRI performed 20 hours after admission.
A: Diffusion weighted images (DWI) showed hyperintensity along the wall of inferior horn of right lateral ventricle.
B,C: Fluid-attenuated inversion recovery (FLAIR) images showed hyperintense signal changes in the right mesial temporal lobe and hippocampus with slight hippocampal atrophy. These findings indicated right lateral ventriculitis and encephalitis mainly on right mesial lobe and hippocampus.
D: T2-weighted image showed pan-paranasal sinusitis.

FACTORS ASSOCIATED WITH VIRAL INVASION

General neurological complaints reported in COVID-19 include dizziness (16.8%) and headache (8%–34%).

An encephalopathy or an acute multifactorial delirium is found in more than 25% of ICU patients.

Predisposing factors include

1. ***Prolonged hospital and ICU stays and compounded by the relative isolation***
2. ***Direct CNS viral invasion***
3. ***Effects of multiorgan failure***
4. ***Social and environmental isolation during ICU care as well as unusual positions for respiratory care including prone positioning.***
5. ***Underlying comorbidities .***

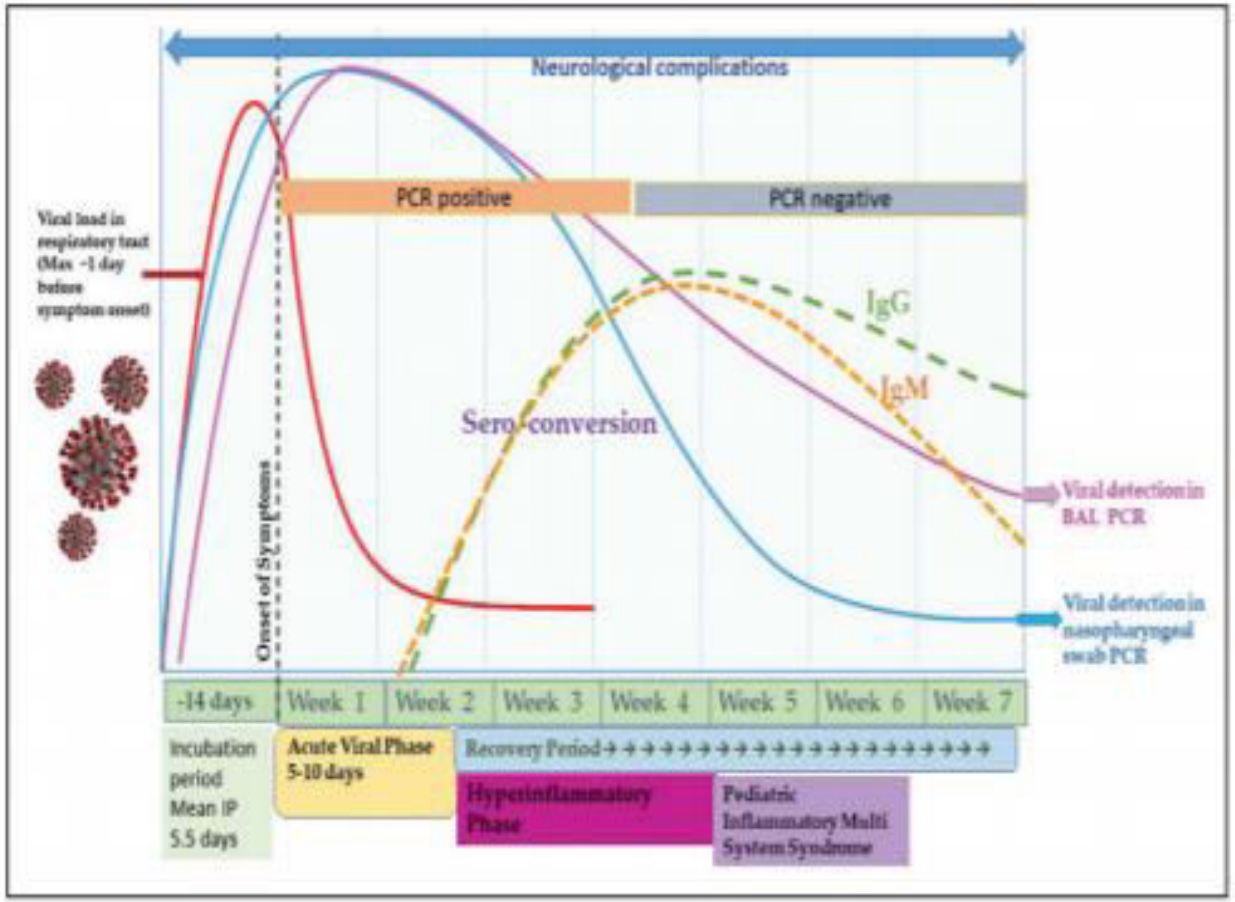
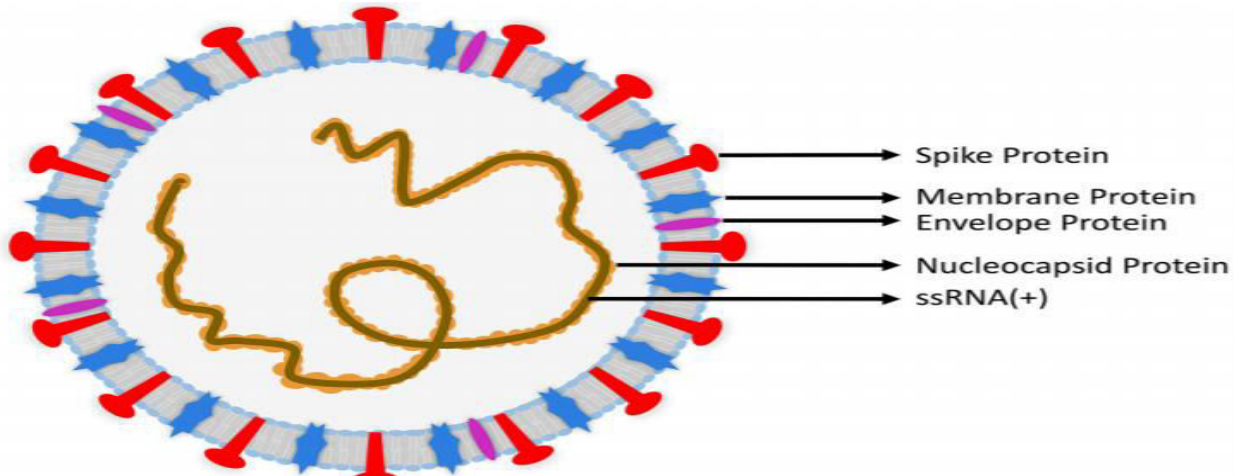


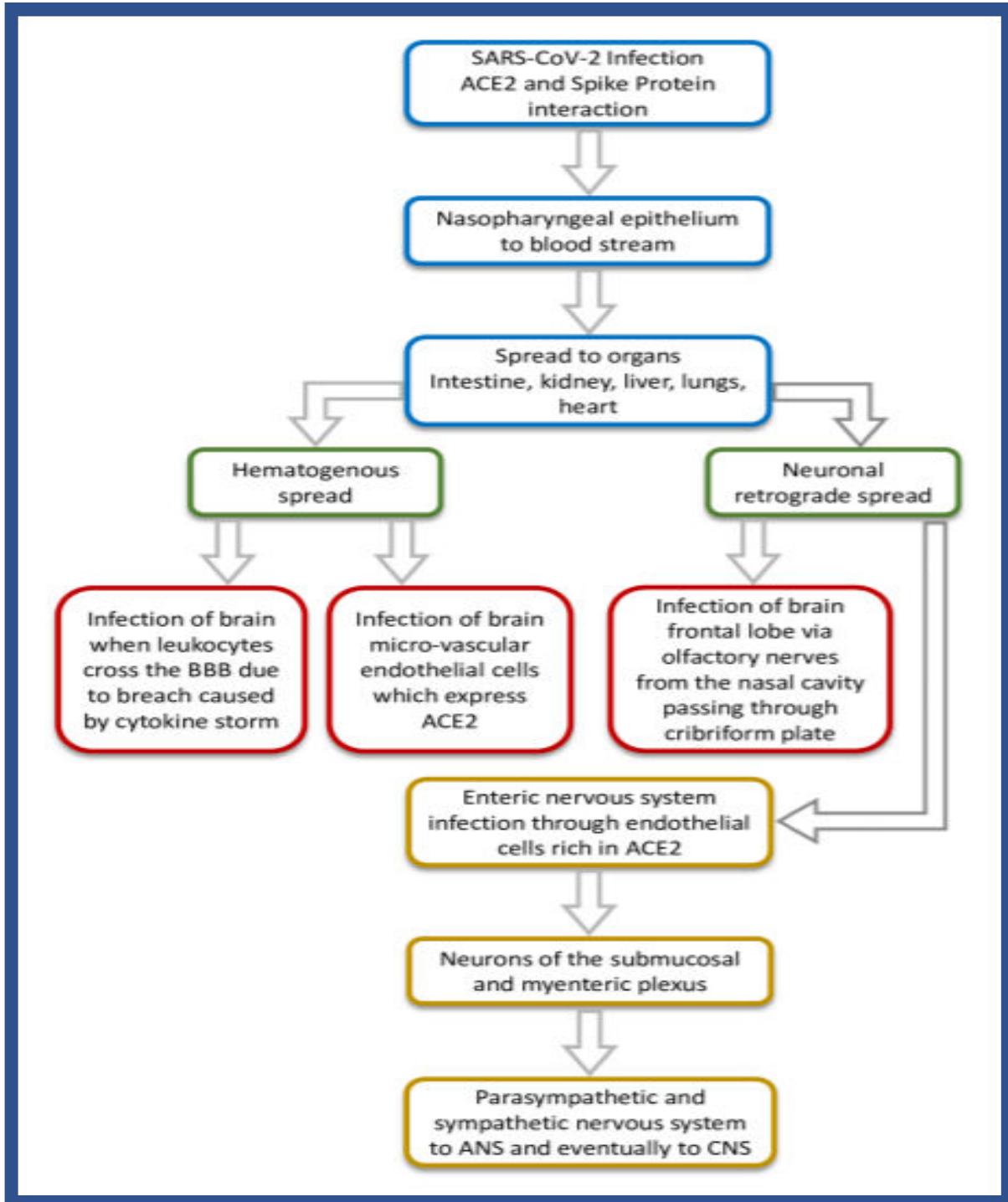
Figure 1: Graph showing the interaction of the viral and host response in patients with COVID-19

POSSIBLE ROUTES OF NEUROINVASION BY SARS-CoV-2

SARS-CoV-2 uses the spike protein to interact with the host ACE2 receptor expressed in various tissues and serves as the entry point for the virus

Apart from ACE2 , SARS-CoV-2 also uses TMPRSS2 as well as endosomal cysteine proteases to assist S – Protein binding .





PATHOPHYSIOLOGY OF CNS INVOLVEMENT

SARS-CoV-2 INVASION

- Direct infection injury
  - Haematogenous pathway
    - Myeloid cell trafficking
      Cytokine release
      Endothelial damage in BBB
  - Neural pathway
    - Demyelination
      Neuroinflammation
- Hypoxic injury
  - Anaerobic metabolism
- ACE2
- Immune injury
  - SIRS
- Hypercoagulability
  - Elevated D-dimer

BBB = Blood brain barrier
ACE2 = Angiotensin-converting enzyme 2
SIRS = Systemic inflammatory response syndrome

- Infectious toxic encephalopathy
- Viral encephalitis
- Acute cerebrovascular disease

PATHOPHYSIOLOGY OF CNS INVOLVEMENT

SARS-CoV-2 can take two pathways to involve the brain ; Direct and Indirect pathways

Postulated Direct Pathways

1. The hematogenous route
2. Neuronal transport
3. Olfactory network
4. Respiratory network
5. Gut-Brain Axis

Postulated Indirect Mechanisms

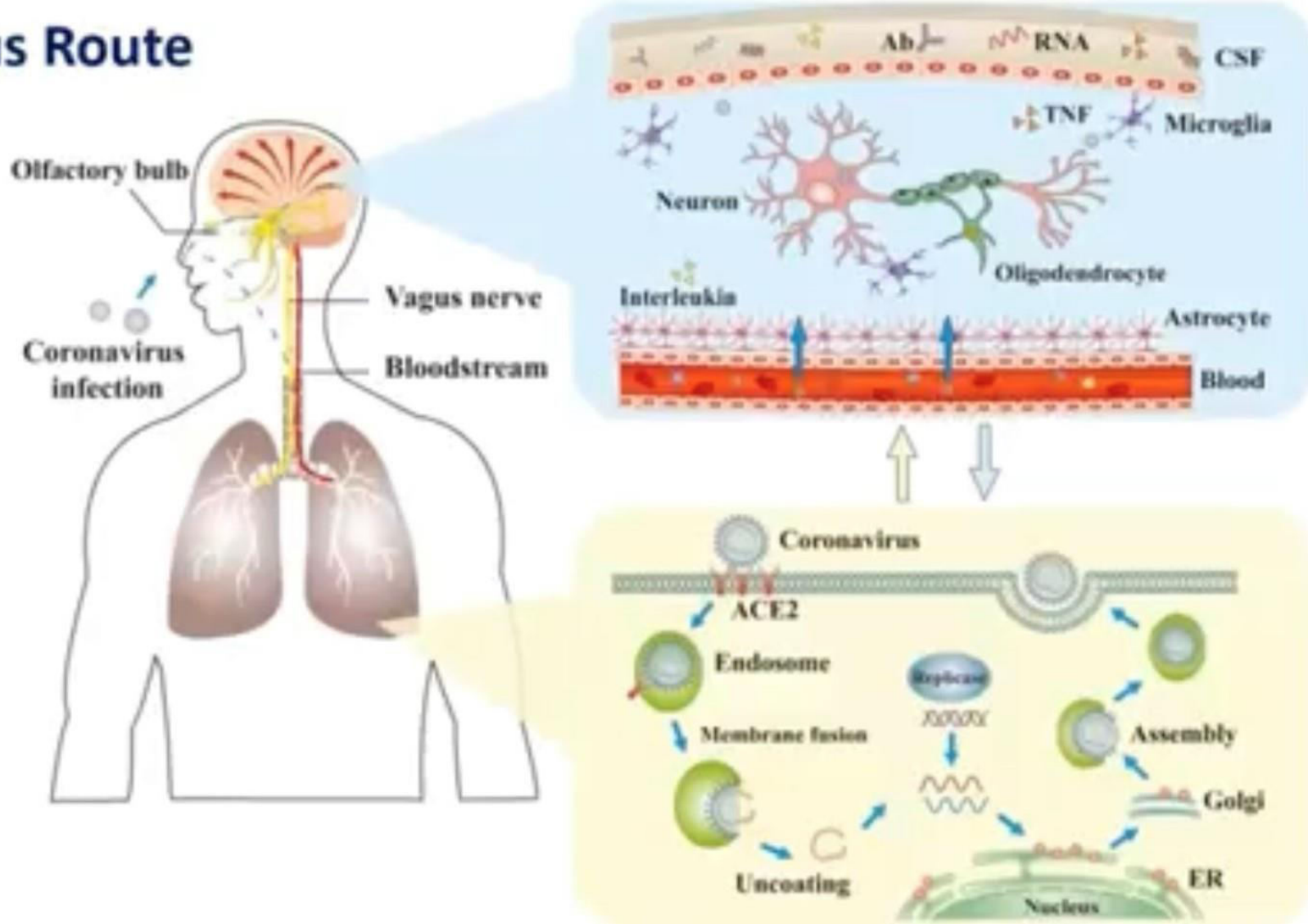
1. Cytokine dysregulation
2. Peripheral immune cell transmigration
3. Neuroinflammation
4. Post-infectious autoimmunity
5. Hypoxic-injury
6. Immunomodulatory treatments
7. Gut-Microbiome translocation
8. ACE-2 receptor involvement
9. Hypercoagulability

HAEMATOGENOUS ROUTE

Most likely pathway for SARS-CoV-2 to the brain .

Virus gains access by infecting endothelial cells of the blood-brain barrier , epithelial cells of blood – CSF barrier in the choroid plexus , or using inflammatory cells as Trojan horses to gain access to CNS (myeloid cell trafficking)

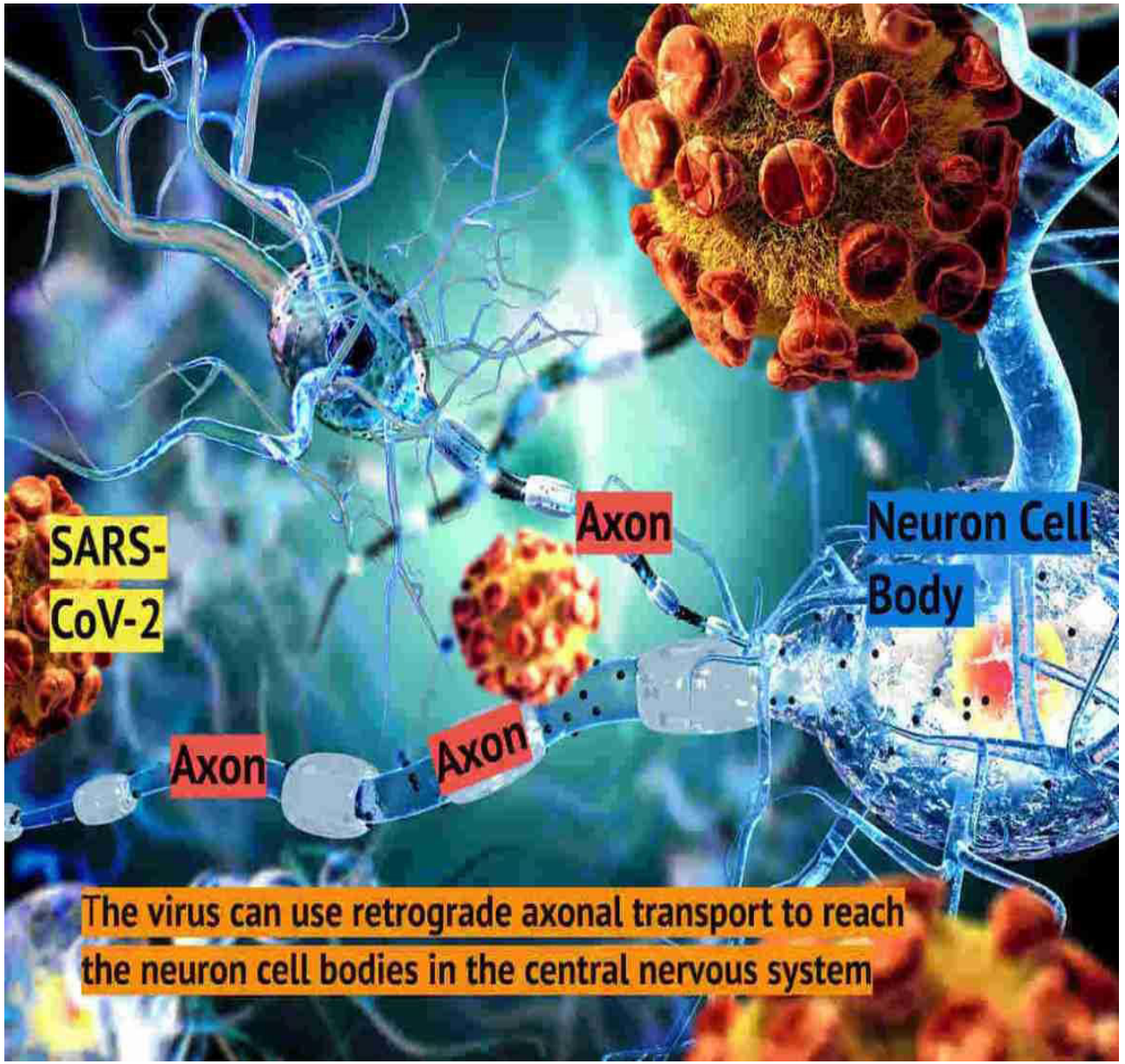
Demonstrated by the observation of viral-like particles in brain capillary endothelium and active budding across endothelial cells.



NEURONAL TRANSPORT

The virus can use retrograde axonal transport (travel from axon terminals across the axon) to reach the neuron cell bodies in the central nervous system

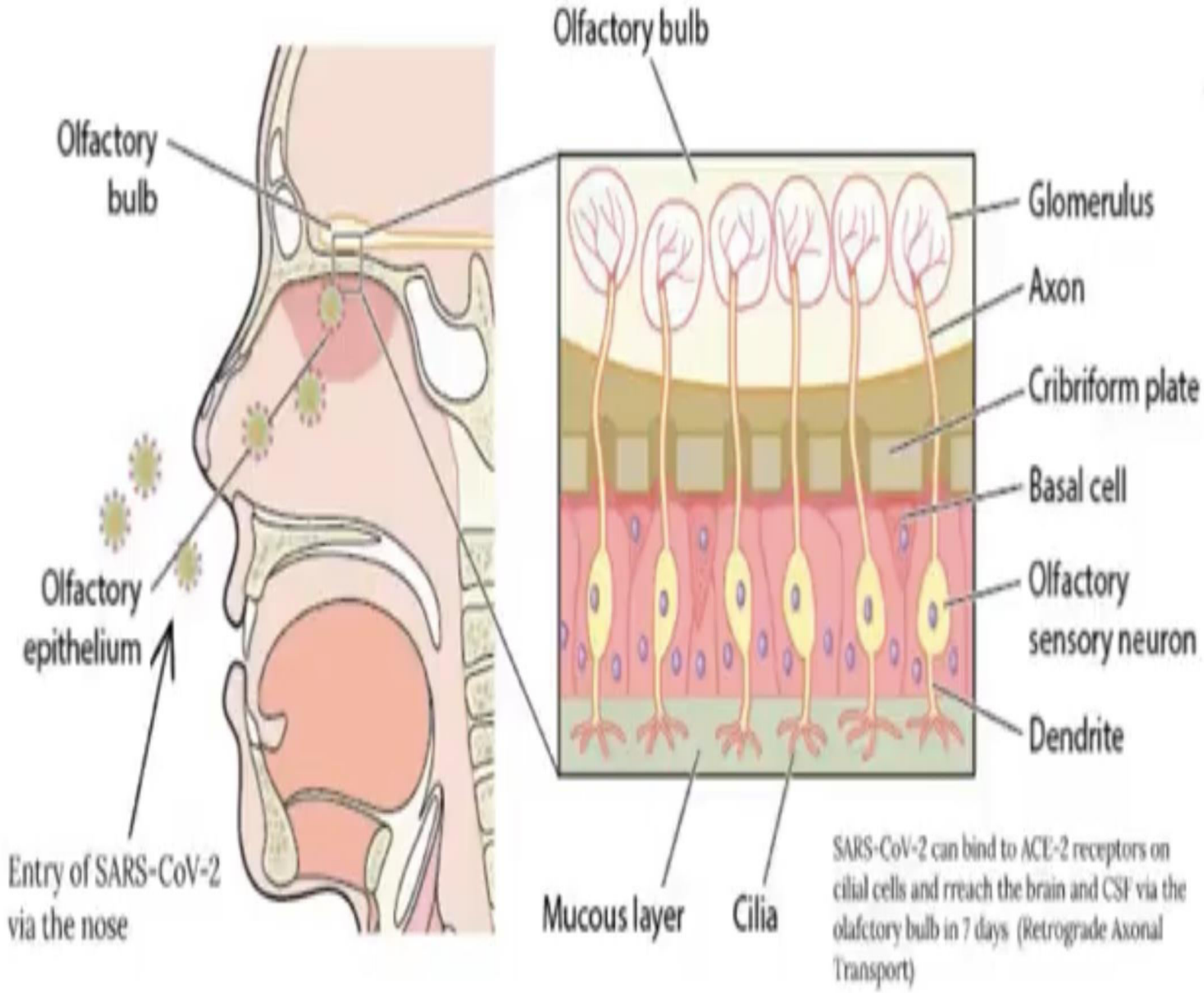
Retrograde axonal transport may occur through olfactory , respiratory , and enteric nervous system networks



OLFACTORY NETWORK

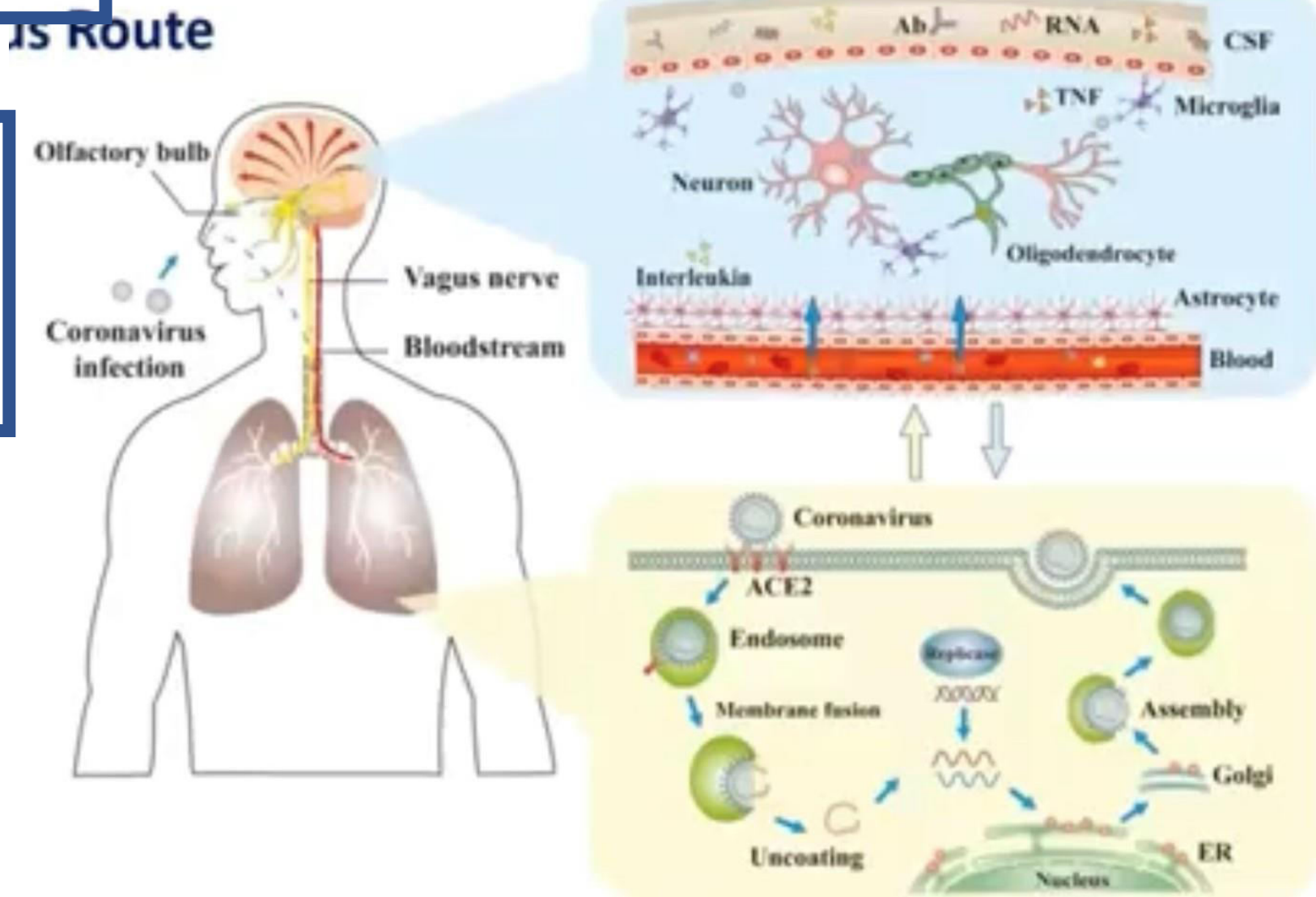
Retrograde neuronal transport via the olfactory pathway (across the cribriform plate of the ethmoid bone to the olfactory bulb situated in the forebrain) is a likely route given the proximity to the brain but also due to the presence of ACE2 receptors on olfactory cilial cells

Virus can reach the CSF and brain through olfactory nerve and bulb within 7 days and can cause inflammation and a demyelinating reaction



RESPIRATORY NETWORK

Virus enter via retrograde neuronal transport via axons from the peripheral nerves of the respiratory network in the medulla oblongata , where respiratory rhythm is generated and regulated



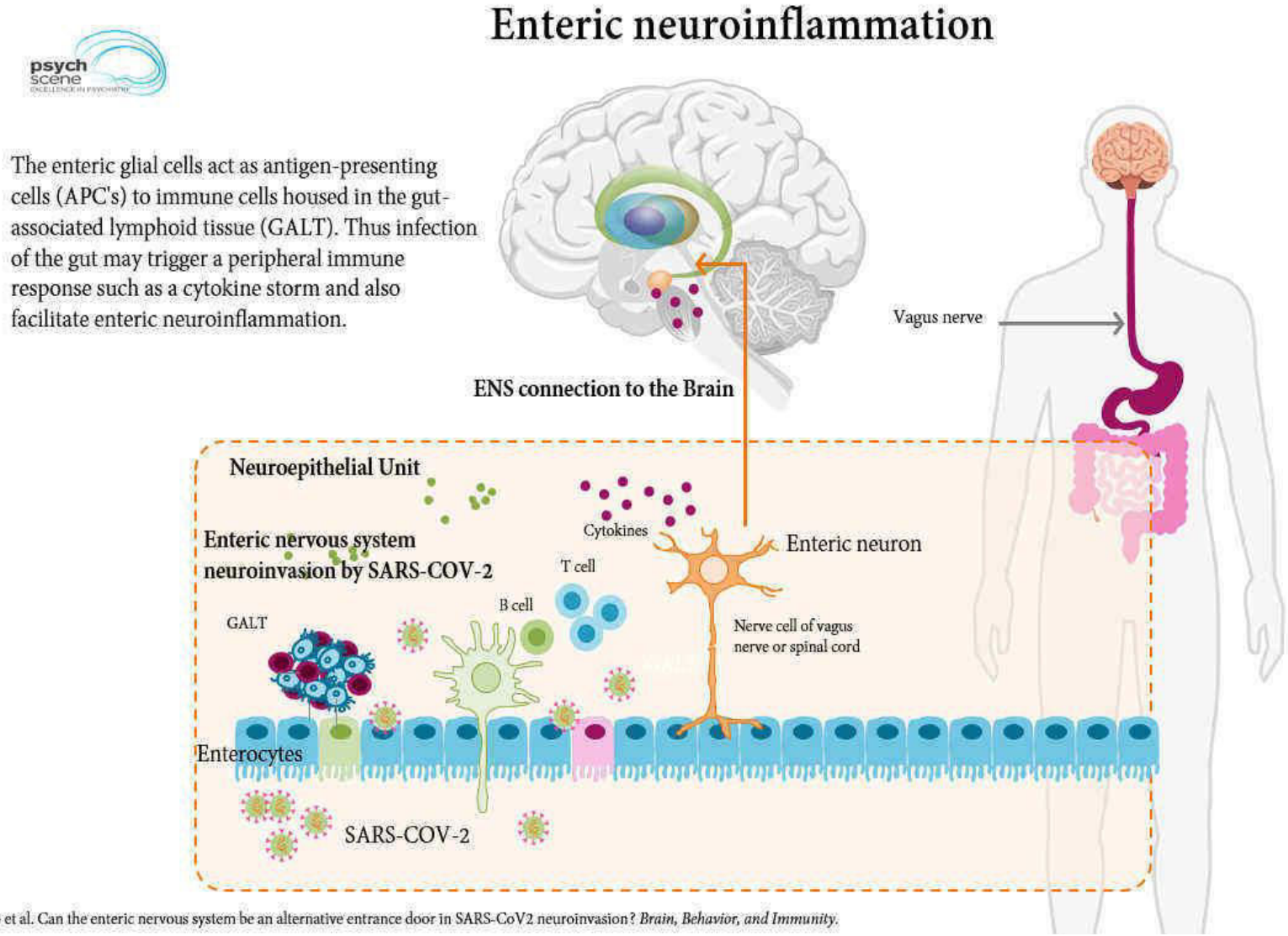
GUT-BRAIN AXIS

- *Viral shedding in faeces is known to occur up to 5 weeks post infection.*
- *GUT – key entry point due to*

1.Higher relative expression of ACE-2 receptor in enterocytes than lungs

2. SARS-CoV2 can directly infect and replicate in intestinal cells.

- *Enterocytes are connected to the enteric nervous system and provide a source of entry to the brain.*
- *Enteric glial cells act as APC's to immune cells housed in GALT .*
- *An infection of gut may trigger a peripheral immune response such as cytokine storm and also facilitate enteric neuroinflammation*

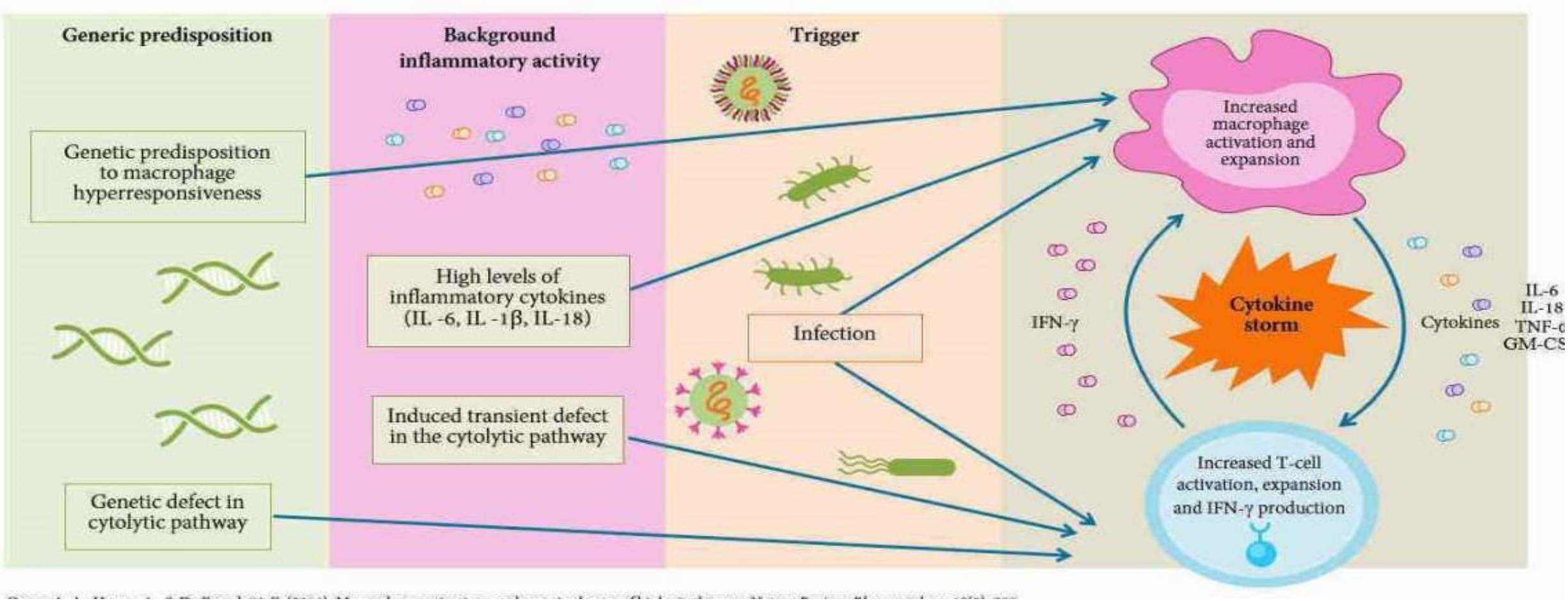


Esposito, G et al. Can the enteric nervous system be an alternative entrance door in SARS-CoV2 neuroinvasion? *Brain, Behavior, and Immunity.*

POSTULATED INDIRECT MECHANISMS OF BRAIN INVOLVEMENT

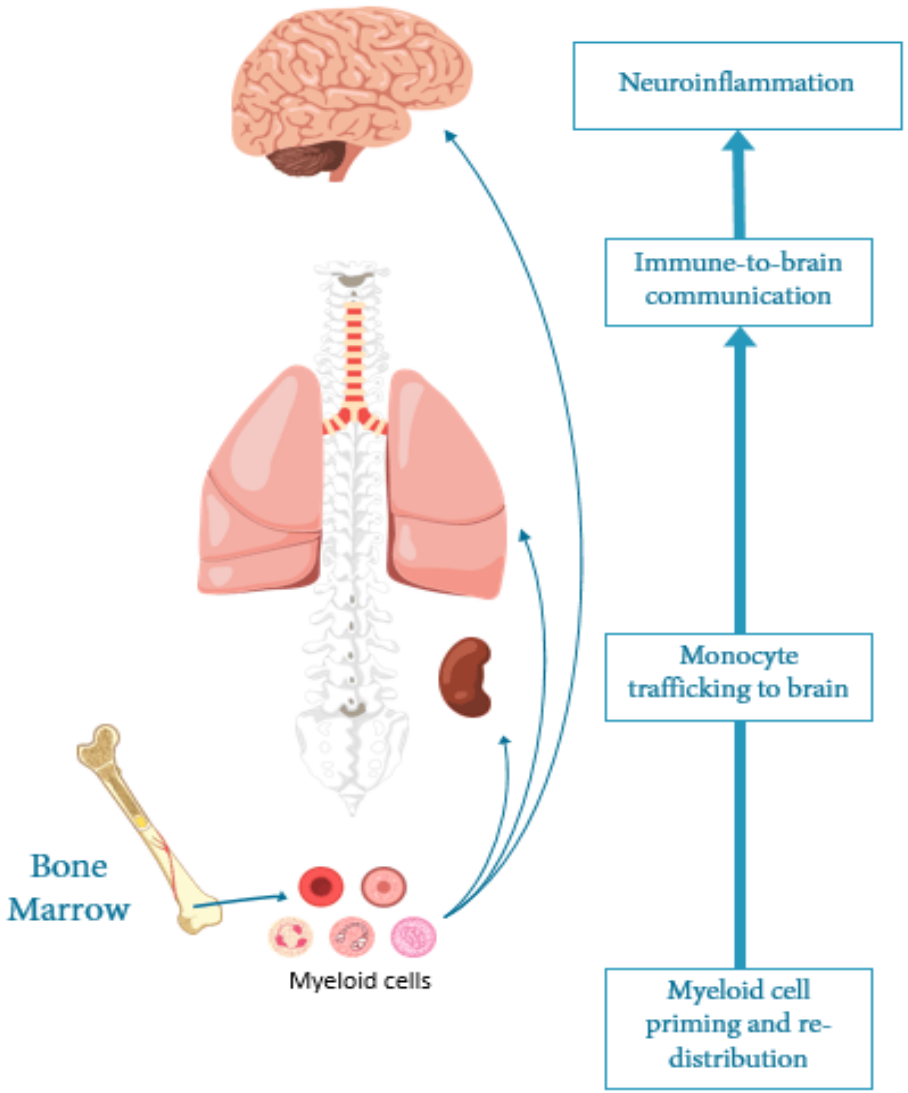
CYTOKINE DYSREGULATION

Proinflammatory cytokines(IL-6 & TNF-α) are significantly higher among deceased COVID-19 patients , which have been linked to CYTOKINE STORM- RELATED ENCEPHALITIS .



PERIPHERAL IMMUNE CELL TRANSMIGRATION

Human coronavirus may play a possible role in the development of neurological symptoms via the opportunistic infection of peripheral myeloid cells(Trojan Horse mechanism) , which are then trafficked to the brain causing neuroinflammation and virus induced neuropathology .

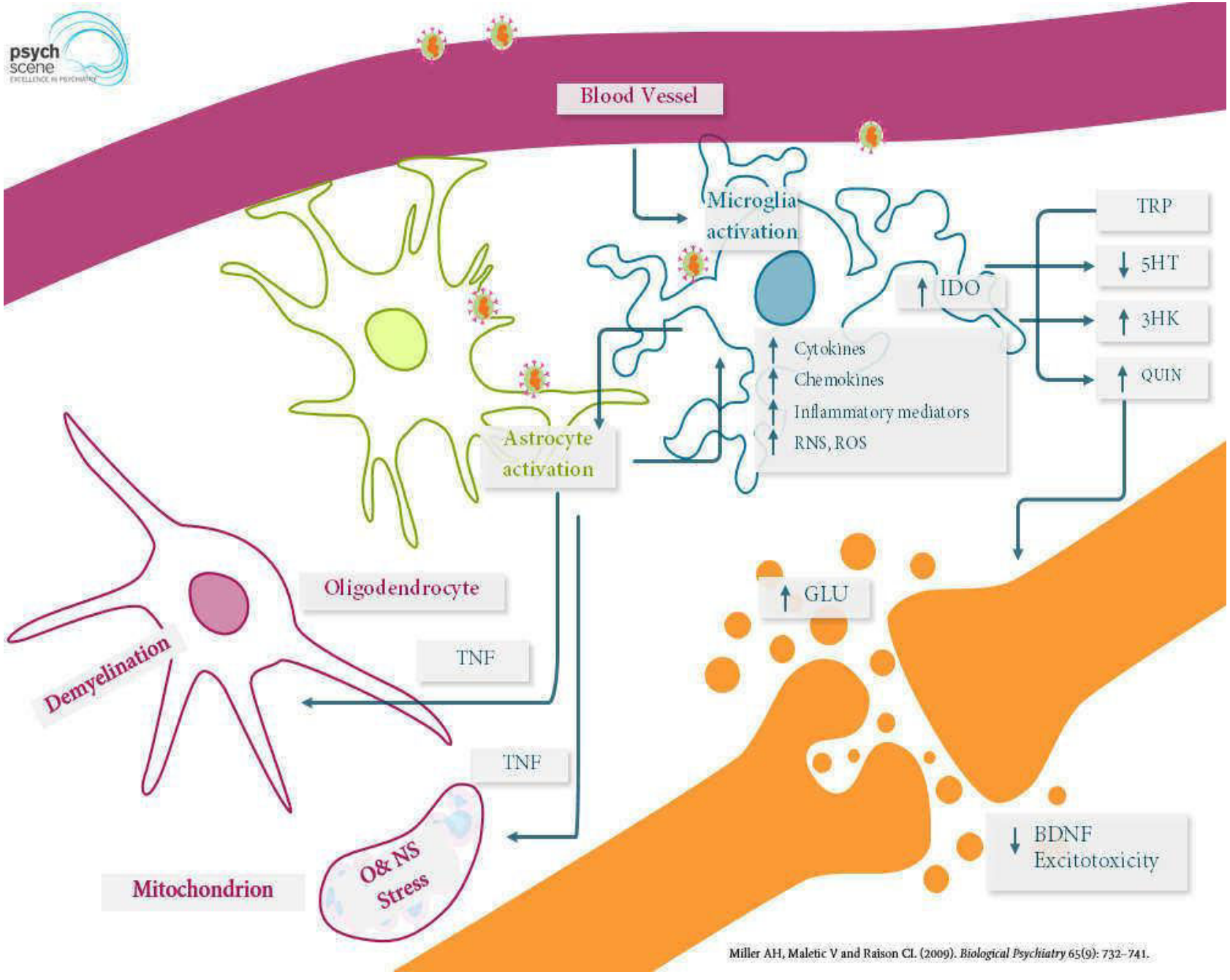


Ingersoll, M. A., Platt, A. M., Potteaux, S., & Randolph, G. J. (2011). Monocyte trafficking in acute and chronic inflammation. *Trends in immunology*, *32*(10), 470-477.

NEUROINFLAMMATION

Cytokines released through peripheral inflammation may increase the permeability of the BBB providing a pathway for the virus to enter the brain.

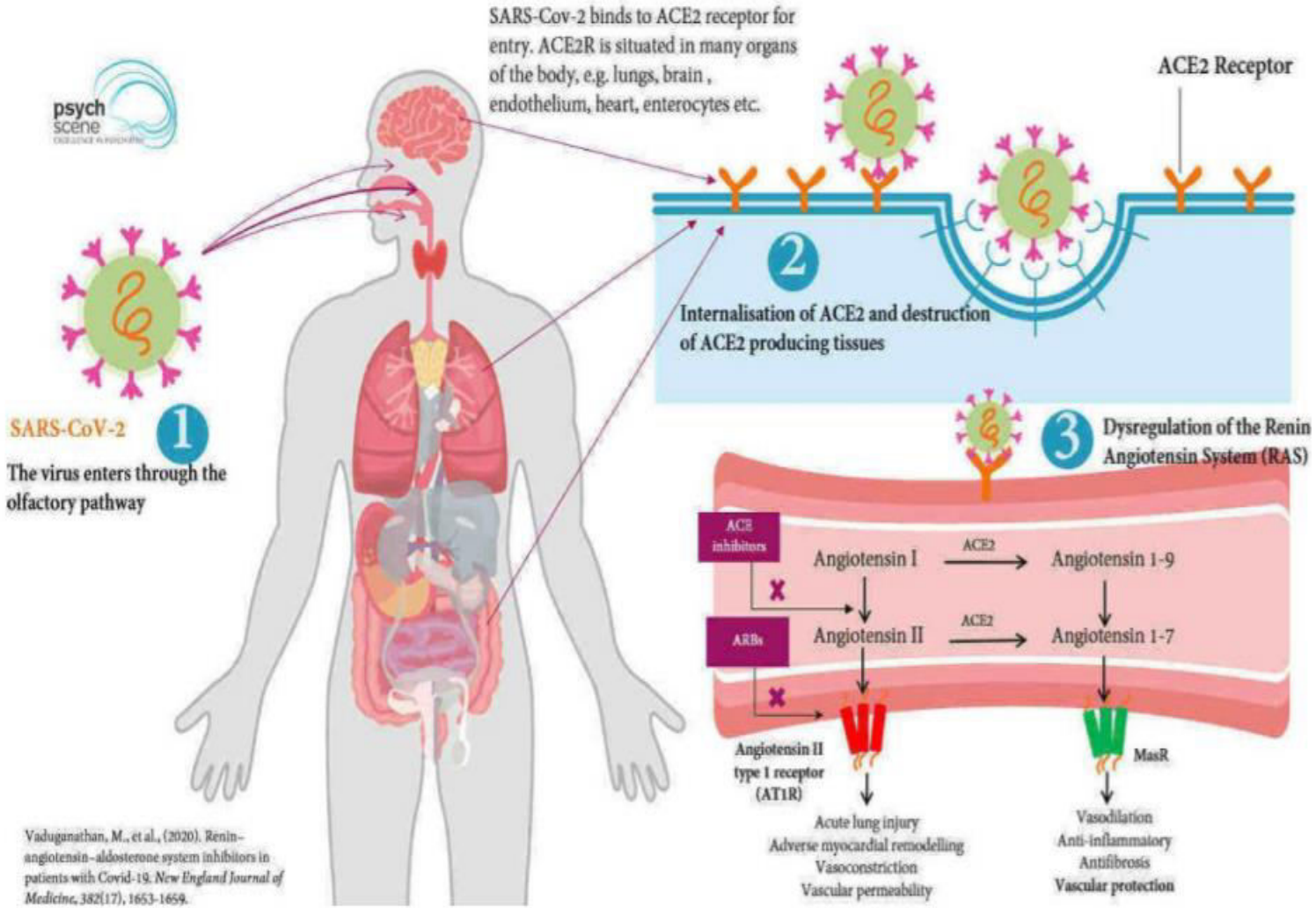
Once in the CNS , it can infect astrocytes and microglia activating the cascade of inflammation and neurodegeneration through release of TNF , cytokines , ROS and other inflammatory mediators

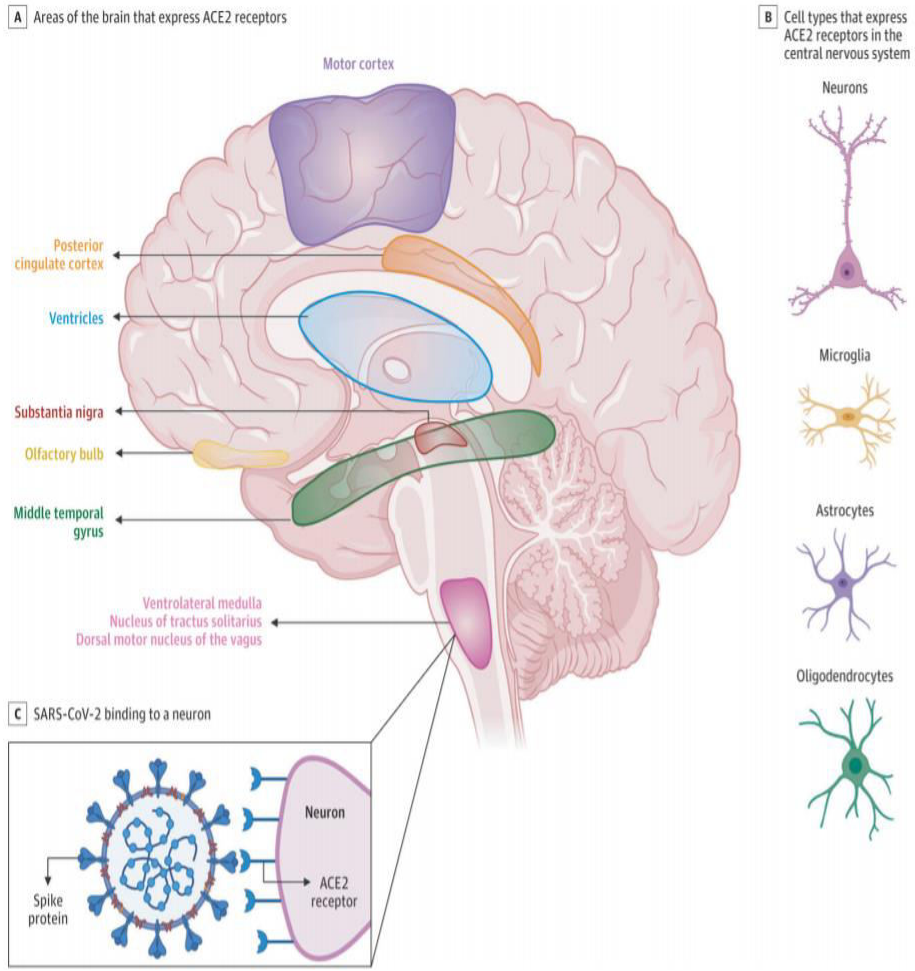


Miller AH, Maletic V and Raison CL (2009). *Biological Psychiatry* 65(9): 732–741.

ACE-2 RECEPTOR INVOLVEMENT

Loss of ACE-2 leads to the functional deterioration of heart and progression of cardiac , renal and vascular pathologies





POST-INFECTIOUS AUTOIMMUNITY

- *Viral infections induce auto-reactive processes that potentiate the development of an autoimmune response in susceptible individuals .*

- *Mechanisms of CNS Autoimmunity include :*

1. *Molecular mimicry*
2. *Bystander activation of immune cells*
3. *Epitope spreading*

HYPOXIC INJURY

- *Hypoxia in the brain may occur via direct infection of the lung tissue but may also occur due to neuroinvasive potential of the virus directly affecting the medullary cardiorespiratory centre.*

- *Hypoxia of brain increases anaerobic metabolism in the mitochondria of the brain cells , and the resultant lactic acid leads to cerebral oedema , reduced blood flow , raised intracranial pressure , presenting with a range of neuropsychiatric symptoms*

GUT MICROBIOME TRANSLOCATION

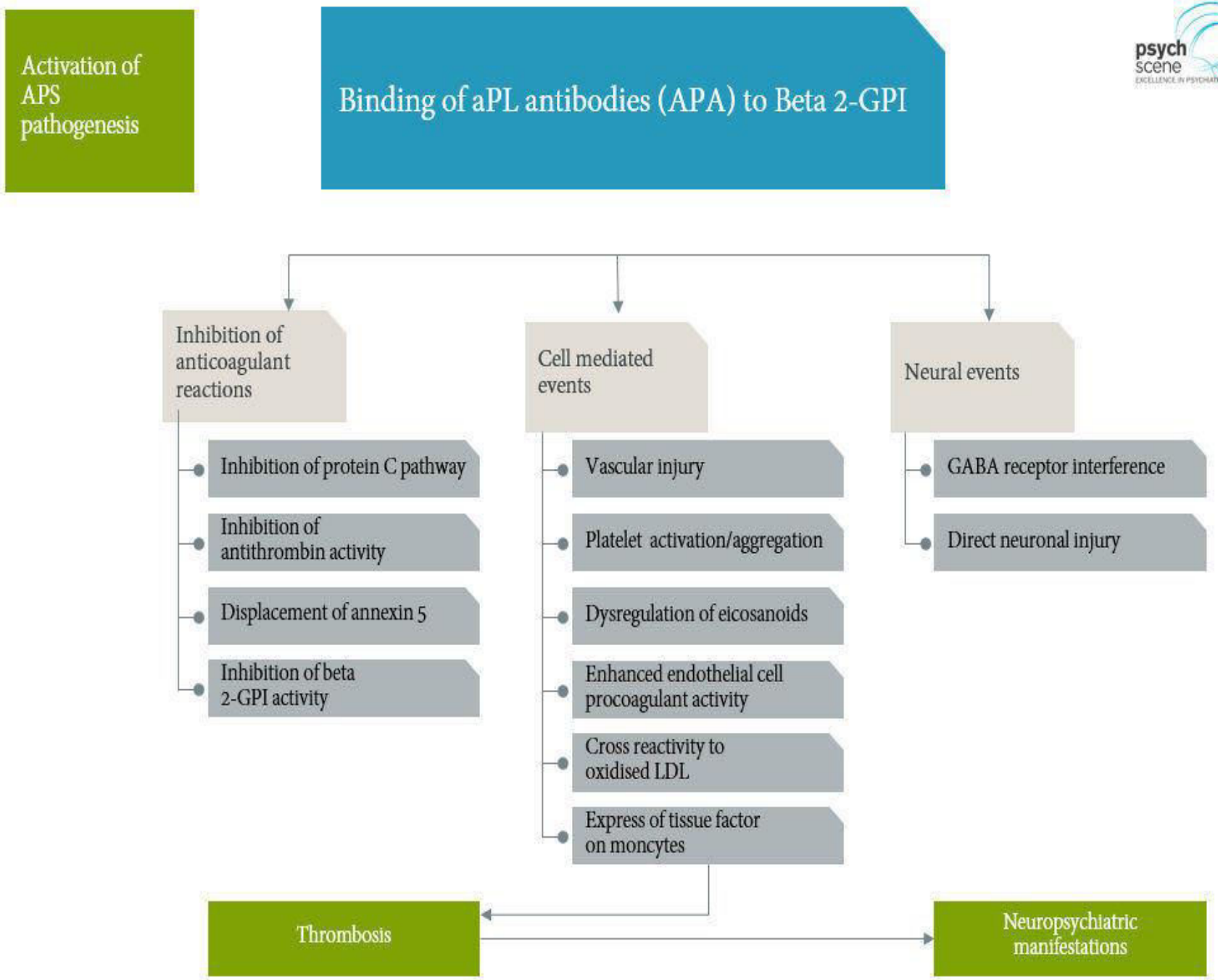
Inflammation disrupts the intestinal barrier resulting in ' gut leak ' causing bacterial translocation into circulation and secondary systemic infection .
Increased intestinal permeability leads to influx of large amounts of lipopolysaccharides which in turn causes the release of TNF-α , IL-1β , & IL-6 , further exacerbating systemic inflammation

IMMUNOMODULATORY TREATMENTS

Use of high dose corticosteroids during acute phase is linked to acute neuropsychiatric effects such as sleep disturbances , delirium , mania , depression and psychosis .

HYPERCOAGULABILITY

Persistent inflammatory status in severe and critical COVID-19 acts as an important trigger for the coagulation cascade .
MECHANISMS :
1 . IL-6 , could activate the coagulation system and suppress the Fibrinolytic system.
2 . Pulmonary and peripheral endothelial injury due to direct viral attack.
3 . Endothelial cell injury activate the coagulation system by the exposure of tissue factor and other pathways.
4 . Dysfunctional coagulation exacerbate an aggressive immune response setting up a vicious cycle .



Rege, S., & Mackworth-Young, C. (2015). Antiphospholipid antibodies as biomarkers in psychiatry: review of psychiatric manifestations in antiphospholipid syndrome. Translational Developmental Psychiatry, 3(1), 25452.

NEUROLOGICAL MANIFESTATIONS

Beginning primarily as a Respiratory illness with Flu like symptoms subsequently affecting Neurological and other systems of the body .

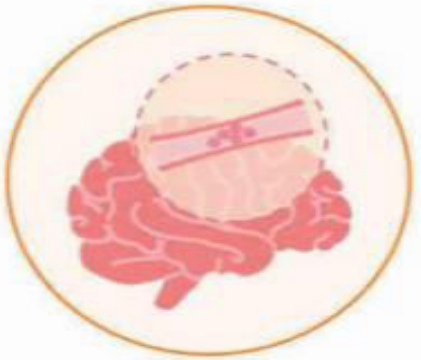
Apart from the Neurological aspects and Manifestations , we shall review the

1. *Impact of COVID-19 on patients with pre-existing neurological disorders*
2. *Impact of drugs used to treat COVID-19 and their potential affects on Nervous system.*
3. *Effect of the pandemic on practice of neurology .*

NEUROLOGICAL MANIFESTATIONS

Encephalopathies
Meningoencephalitis
Neuromuscular disorders
Psychiatric disorders
? Neurodegenerative disorders

Anosmia
and Ageusia



Acute Cerebrovascular Disease

Infectious Toxic Encephalopathies (Hypoxia, metabolic disturbance and systemic inflammation)

Neurological Manifestations

CNS MANIFESTATIONS

- *Headache , Giddiness*
- *Seizures*
- *Encephalopathies*
- *Encephalitis*
- *Acute disseminated encephalomyelitis*
- *Myelitis*
- *Stroke – Ischemic , Haemorrhagic*
- *CVT*
- *CNS Vasculitis*

PNS MANIFESTATIONS

- *Guillain-Barre syndrome and variants*
- *Cranial Neuropathies*
- *Neuropathic pain*
- *Anosmia , Ageusia*
- *Rhabdomyolysis*
- *Myopathy*

Neurological Manifestations

HEADACHE :

- *Common initial symptom of COVID-19*
- *ETIOLOGY :*
- *Increased stress , excessive anxiety , changes in lifestyle*
- *Systemic viral infection , primary cough headache , and tension-type headache*
- *PPE-Associated headache .*
- *Treatment : Acetaminophen*

SEIZURES

- *Convulsive & Nonconvulsive status epilepticus triggered by SARS-CoV-2 virus*
- *Etiology : Hypoxia , metabolic derangements , organ failure , or cerebral damage .*

ENCEPHALOPATHY

***CLINICAL FEATURES** : Delirium , Agitation , Somnolence , Seizures , Dysexecutive syndrome*

MECHANISM :

- *Hypoxia , dysregulated systemic immune response*
- *High levels of circulating proinflammatory cytokines can damage blood brain barrier , especially in temporal lobes .*
- *Metabolic derangements from organ failure*
- *Medication effects*

ADEM

- *The pro-inflammatory state induced by the cytokine storm(IL-6 , IL-1 , & TNF-α) – glial cell activation with subsequent demyelination .*
- *Para-infective or post-infective phenomenon – Virus triggered antibodies against glial cells*
- *SARS-CoV-2- infective trigger (like Epstein Barr virus in MS)*

ACUTE NECROTIZING ENCEPHALITIS

COVID-19–associated Acute Hemorrhagic Necrotizing Encephalopathy: Imaging Features

Neo Poyiadji, MD • Gassan Shahin, MD • Daniel Noujaim, MD • Michael Stone, MD • Suresh Patel, MD • Brent Griffith, MD

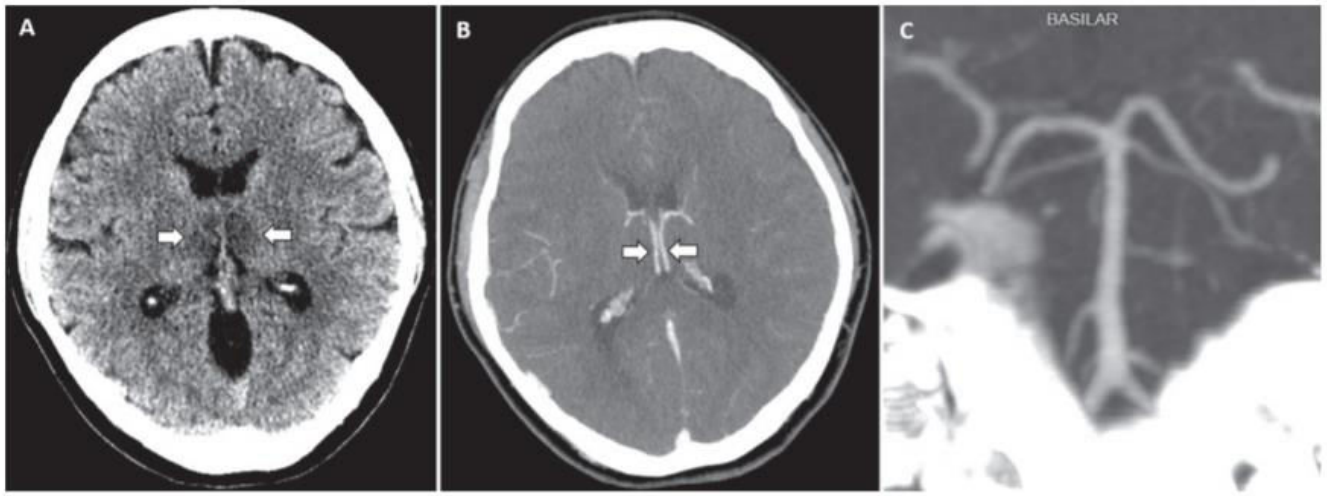


Figure 1: A, Unenhanced CT scan of head demonstrates symmetric low attenuation within the bilateral medial thalami (arrows). B, Axial CT venogram demonstrates patency of the cerebral venous vasculature, including the internal cerebral veins (arrows). C, Coronal reformation of CT angiogram demonstrates normal appearance of the basilar artery and proximal posterior cerebral arteries.

- *Acute necrotizing encephalopathy is a rare complication of influenza and other viral infections and has been related to intracranial cytokine storms, resulting in blood-brain barrier breakdown without direct viral invasion or parainfectious demyelination .*
- *Characteristic imaging feature includes symmetric, multifocal lesions with invariable thalamic involvement .*
- *Other commonly involved locations include the brainstem, cerebral white matter, and cerebellum*

- *A 58 y / Female*
- *H/O Cough / Fever / altered sensorium*
- *RT-PCR Positive(nasopharyngeal swab)*
- *CSF RT-PCR not done*
- *Treated with IVIG*

CEREBROVASCULAR DISEASE

ISCHEMIC STROKE

- Most commonly reported complication of COVID-19.
- Stroke onset 1-3 weeks after COVID-19 SYMPTOMS
- Large vessel strokes are more common in males & younger age.
- No or minimal risk factors for CVA & severe COVID-19.
- MECHANISMS :
- Thrombophilia leading to hypercoagulability & inflammation .
- Complement activation – thrombotic microvascular injury
- Cytokine storm – elevated D-Dimer , ferritin and elevated proinflammatory cytokines
- Embolic stroke – Cardiac dysfunction (myocarditis or cardiac injury)
- MANAGEMENT :
- The management should follow same standards of care as for patients without COVID-19 , but with necessary precautions related to infection control .

HEMORRHAGIC STROKE

- Relatively young (mean age of 50 years) , lower than for conventional ICH
- Usual location in lobar territories
- Had markedly raised D-dimer values in all patients

CEREBRAL VENOUS THROMBOSIS

- Same clinical features
- All patients had elevated D-Dimer levels
- Favourable outcome
- MANAGEMENT : Anticoagulation with UFH /LMWH : Antiedema measures

CEREBRAL MICROBLEEDS AND LEUKOENCEPHALOPATHIES

Indications for performing neuroimaging :

- Encephalopathy(82.9%)
- Focal weakness(5.7%)
- Aphasia(2.9%)
- Apneic episodes(2.9%)
- Seizures(2.9%)

- **MECHANISMS :** Endothelitis with thrombotic microangiopathy & prolonged respiratory failure & hypoxemia .

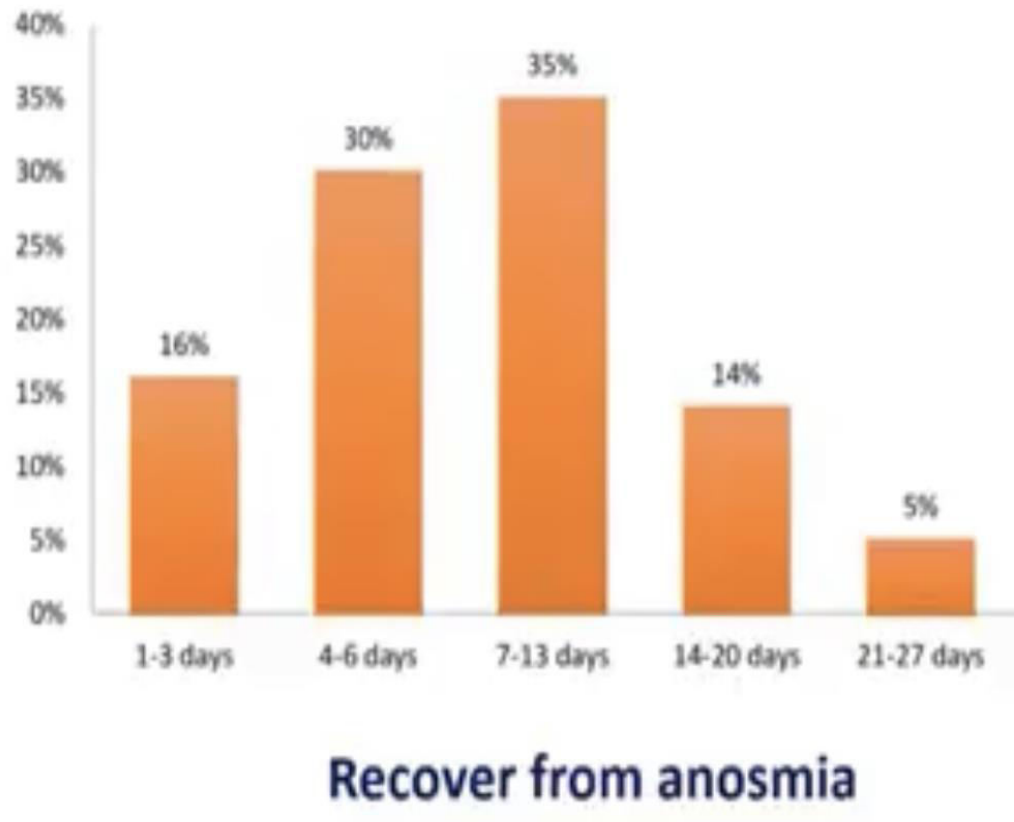
- Presence of leukoencephaloapathy and/or cerebral microbleeds is associated with a critical illness , increased mortality , and worse functional outcome in patients with COVID-19

CRANIAL NEUROPATHIES

- *Bells palsy*
- *Miller Fisher syndrome(MFS)*

- *Ocular motor palsy*
- *Isolated sixth nerve palsy*

- *Anosmia and dysgeusia – common early symptoms(80%) ; due to infiltration of vagus nerve , olfactory network and higher-order chemosensory processing structures in the brain*



GULLIAN BARRE SYNDROME

CLINICAL FEATURES

- *Limb parasthesias or pain and varying degress of extremity weakness were the most common symptoms on presentation*
- *Respiratory muscle paralysis requiring mechanical ventilation in one-third of cases .*

MECHANISM

- *SARS-CoV-2 viral spike(S) protein , binds to ACE-2 & gangliosides containing sialic acid residues*
- *Molecular mimicry*
- *Parainfectious mechanism.*

NCS : Demyelinating(51%) , Axonal(8%)

- *Subtype*
- *AIDP 24(64.8)*
- *AMSAN 5(13.5%)*
- *Miller fisher syndrome 5(13.5%)*
- *AMAN 1(2.7%)*

CSF : Albuminocytological dissociation : 75.8% , pleocytosis : 6.1%

RHABDOMYOLYSIS

- *Raised creatinine kinase with muscle pain in subjects with severe COVID-19*
- *Can present as severe myalgias or muscle weakness with or without associated respiratory symptoms*
- *Creatinine kinase range : 4,000 – 33,000*
- *Raised LDH , CRP , Myoglobin , D-Dimer , hypocalcemia , hyperkalemia and blood in urine*
- *Aggressive treatment with IV Fluids and supportive care for respiratory symptoms*

OTHER COVID-19 RELATED NEUROLOGICAL DISORDERS

NEURODEGENERATIVE DISORDERS

Experience from the past pandemics show that the lag period may be months to years for the onset of neurodegenerative illness when associated .

***PARKINSONS DISEASE** : the Braak hypothesis of Parkinsons disease proposes that a Neurotropic virus invading neural tissue through the nasal cavity and the gastrointestinal tract causes α-synuclenin to be transmitted to key areas such as Substantia nigra .*

NEUROMUSCULAR COMPLICATIONS

Apart from Peripheral neuropathy , Myopathy , GB Syndrome , Other neuromuscular complications described are Myasthenia gravis , transient cortical blindness and Acute disseminated encephalomyelitis

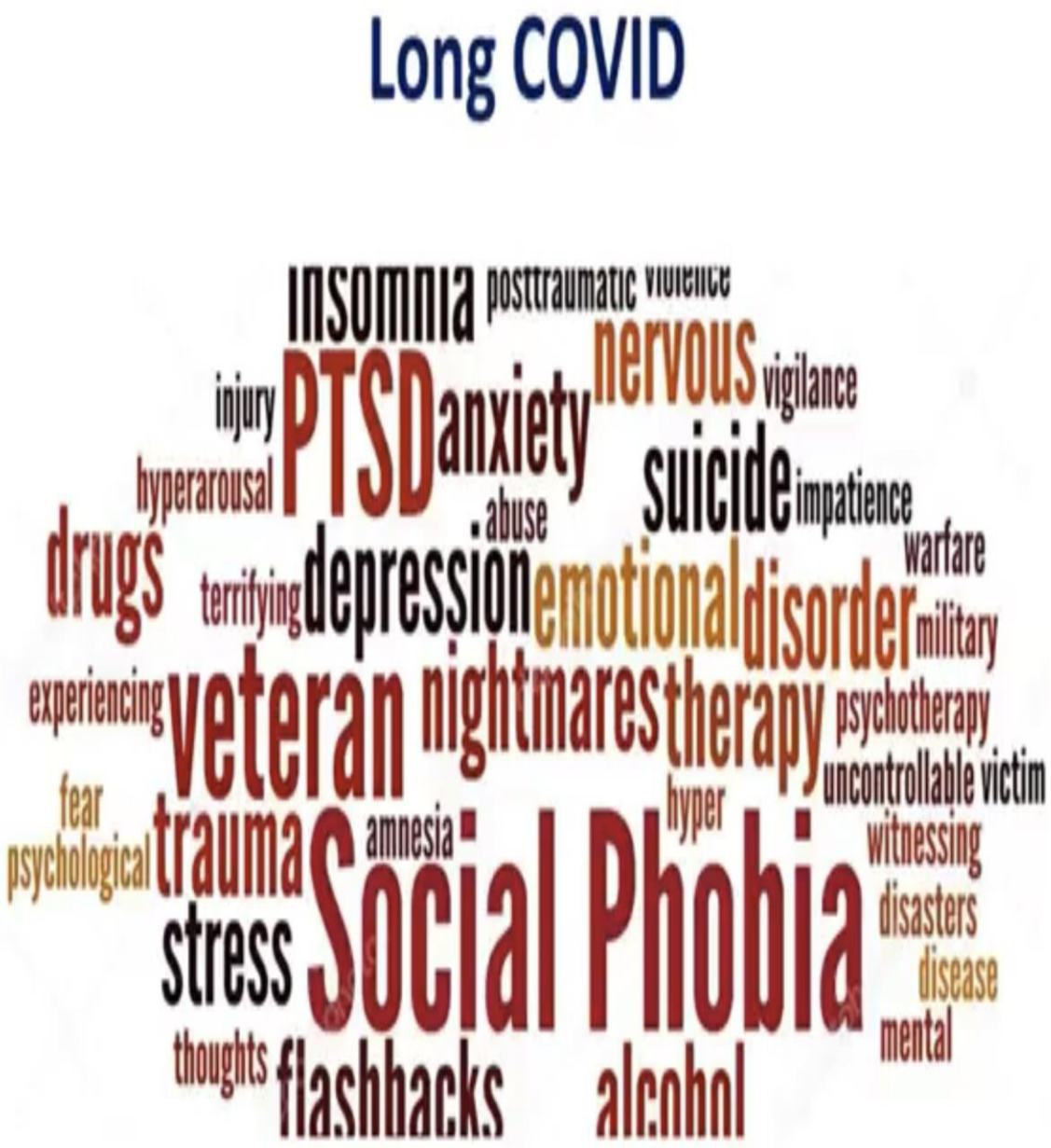
Muscular complications include soreness , fatigue and raised muscle enzymes

NEUROPSYCHIATRIC MANIFESTATIONS

- *Survivors of SARS-CoV-2 were clinically diagnosed with PTSD (54.5%) , Depression (39%) , Pain disorder (36.4%) , Panic disorder(32.5%) , Mood disorders and Obsessive-compulsive disorder(15.6%) post infection , a dramatic increase from their pre-infection prevalence .*

- *Increase in the incidence of first-episode presentations of Schizophrenia and delusional themes related to pandemic .*

- *Higher rates of PTSD in health care workers*



NEUROLOGICAL IMPLICATIONS OF COVID-19 INTERVENTIONS

- ***Given the urgency , many of the therapeutic medications and Vaccinations are being used based on prior experience , or on an experimental basis ,without the benefit of the full gamut of preclinical and clinical trials to test for efficacy or to detect the adverse effects they may cause .***

- ***Many antivirals including Lopinavir , Ritonavir , Chloroquine have been associated with neuropathies and muscle injuries.***

- ***Dexamethasone suggested for the treatment of patients with severe respiratory complications can cause insomnia muscle weakness and behavioural changes .***

- ***So practitioners need to leverage this knowledge to anticipate and monitor for adverse effects , including possible neurological effects , when the drugs are used to treat COVID-19 .***

LONG-HAUL COVID/LONG TAIL COVID

- *Autonomic symtoms in long- haul COVID*

1. *Tachycardia*
2. *Night sweats*
3. *Temperature dysregulation*
4. *Gastroparesis*
5. *Constipation/loose stools*
6. *Peripheral vasoconstriction*

- *CHRONIC FATIGUE SYNDROME*
- *POST TRAUMATIC STRESS DISORDER*
- *BRAIN FOG*

POSSIBLE ETIOPATHOGENESIS OF LONG-HAUL COVID

- *Unmasking of underlying co-morbidities*
- *Residual damage from acute infection*
- *Persistent or restricted viral replication*
- *Persistent immune activation*
- *Unknown cause*

DIAGNOSIS AND BIOCHEMICAL MARKERS OF SEVERITY

INFLAMMATORY MARKERS *are common in severe cases of COVID-19 and appear to corelate with the severity of the symptoms and clinical outcome .*

ELEVATED LEVELS OF INFLAMMATORY MEDIATORS

IL-6 , CRP , S . Ferritin , D-Dimer .
Elevation in Lactic acid levels.
Elevated Troponin levels
Elevated Aminotransferases & LDH
PT/INR Elevation

DECREASED LEVELS OF

LYMPHOCYTES
THROMBOCYTES

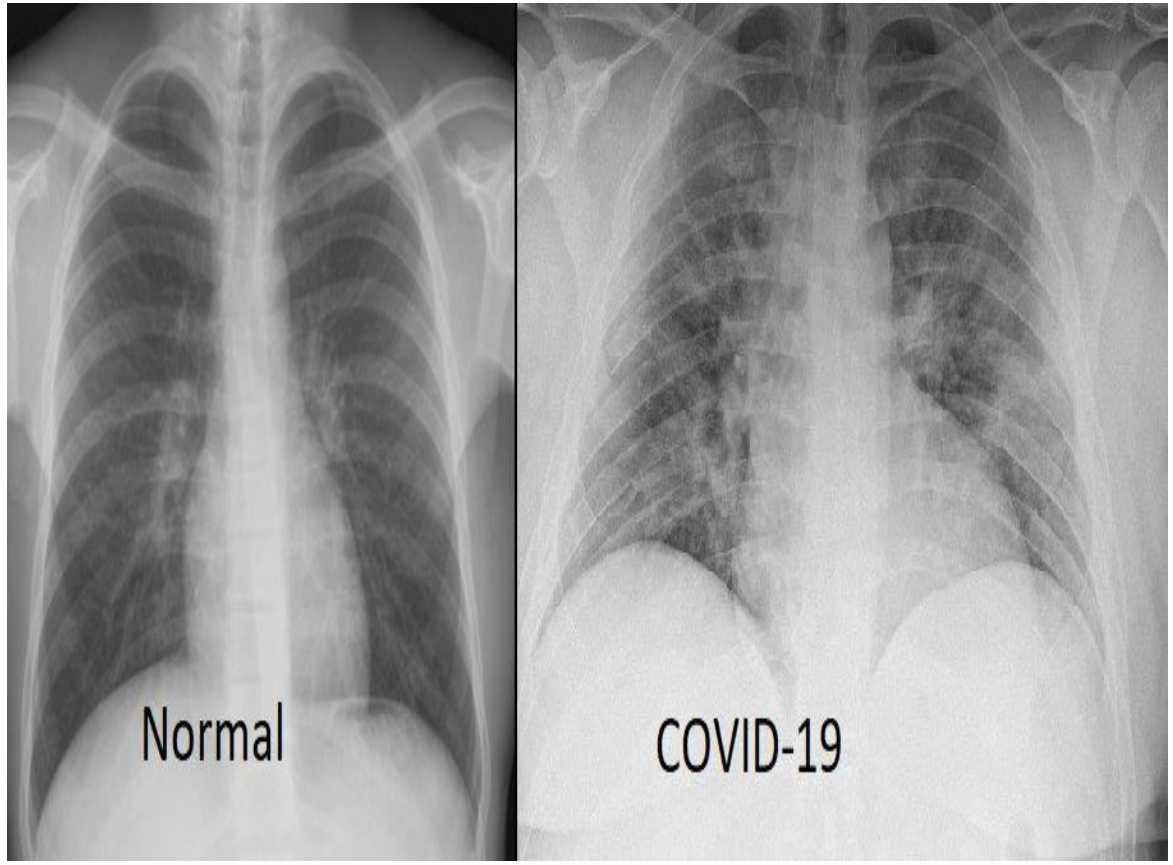
NEUTROPHIL – LYMPHOCYTE RATIO *: Patients aged more than 50 years and with NLR ≥ 3.13 tend to develop severe COVID-19 and should be admitted to ICU .*

IMAGING – CHEST X-RAY

The most frequent findings are airspace opacities

The distribution is most often bilateral , peripheral and lower zone predominant

Findings are most extensive at about 10-20 days after symptom onset



IMAGING – HRCT CHEST

HRCT PATTERN IN COVID-19

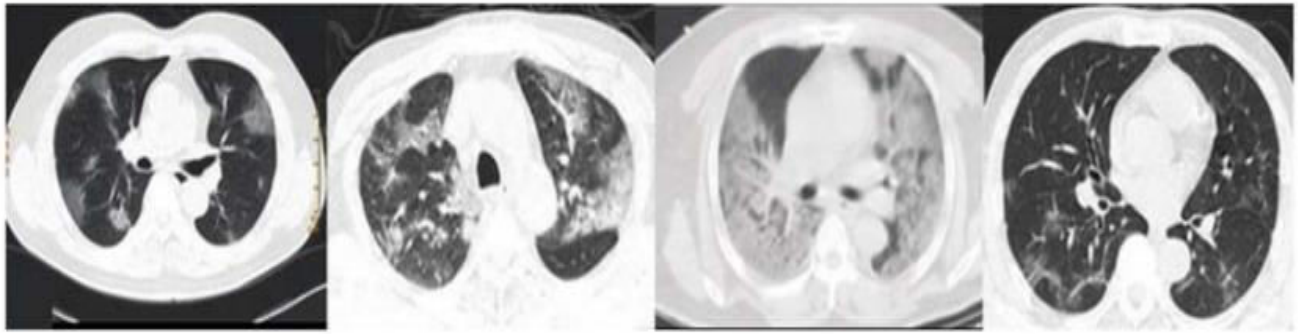
Ground glass opacity	88%
Bilateral involvement	88%
Posterior distribution	80%
Multilobar involvement	79%
Peripheral distribution	75%
Consolidation	35%

CO-RADS*

Level of suspicion COVID-19 infection

		CT findings
CO-RADS 1	No	normal or non-infectious abnormalities
CO-RADS 2	Low	abnormalities consistent with infections other than COVID-19
CO-RADS 3	Indeterminate	unclear whether COVID-19 is present
CO-RADS 4	High	abnormalities suspicious for COVID-19
CO-RADS 5	Very high	typical COVID-19
CO-RADS 6	PCR +	

IMAGING – HRCT CHEST



Early stage

Single or multiple scattered patchy ground-glass opacities, predominately distributed in the peripheral and subpleural area of the lung. A crazy-paving pattern, secondary to intralobular and interlobular septal thickening can be seen in this stage

Advanced stage

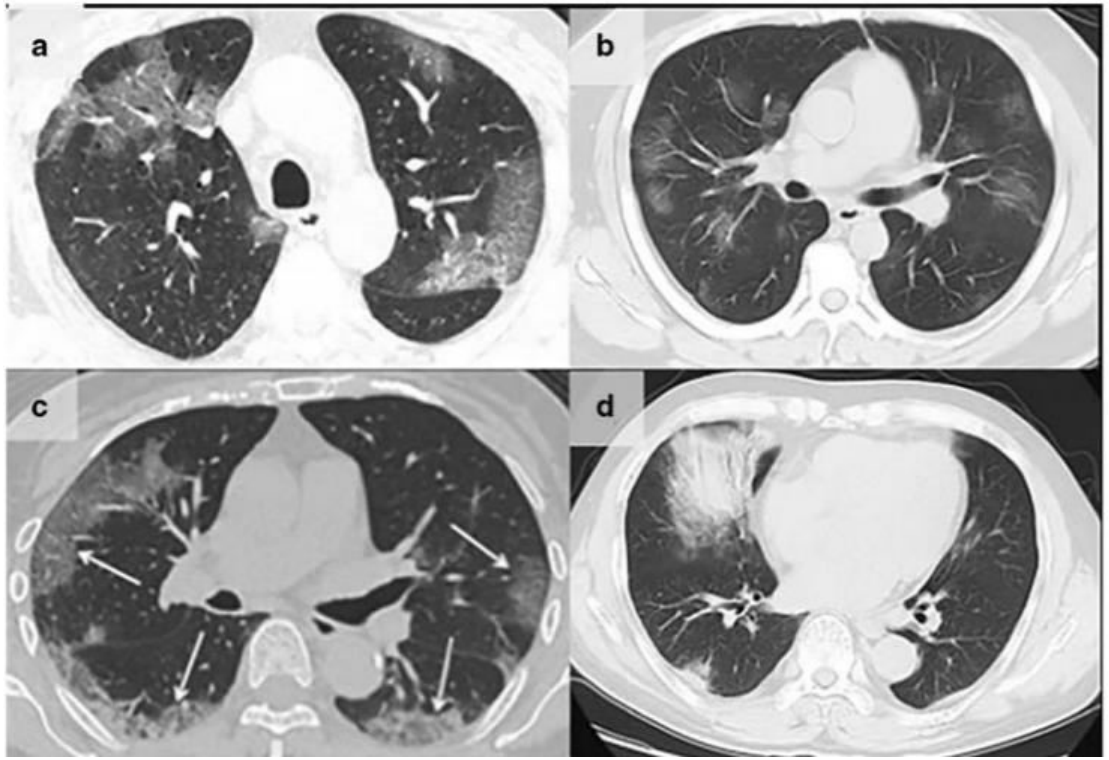
Increased extent and density of bilateral lung parenchymal opacities. In this image, there are both areas of ground glass opacification and areas of consolidation in both lungs, which coexist and have varying sizes and presence of air-bronchogram.

Severe stage

Diffuse consolidation of the lung parechyma with uneven density, air bronchi and bronchial dilation, which may be present as "whited out lung"on a corresponding chest radiograph

Dissipation stage

Areas of ground glass opacity and consolidation have nearly completely resolved, leaving some residual curvilinear areas of density.



SPECIFIC DIAGNOSTIC TESTS FOR COVID-19

NUCLEIC ACID TESTS(INCLUDING RT-PCR)

SEROLOGY (ANTIBODY DETECTION)

ANTIGEN TESTS

EEG : ***In cases of unclear disturbances of consciousness or in cases of epileptic seizures.***

ENMG : ***In diagnosing neuromuscular diseases and guiding treatment***

CSF RT-PCR FOR SARS-CoV-2

In addition to the usual diagnostics for SARS-CoV-2, a RT-PCR test from CSF should also be performed if clinical suspicion of encephalitis, delirium or polyneuritis exists and there are no contraindications against lumbar puncture

CSF IgG ,IgM synthesis .

NEUROIMAGING : CT SCAN OF BRAIN

MRI BRAIN & PERFUSION IMAGING

COMMON FINDINGS ON MRI & PERFUSION IMAGING :

- ***Cortical signal abnormalities on FLAIR images***
- ***Leptomeningeal enhancement***
- ***Bilateral frontotemporal hypoperfusion***
- ***Focal hyperintensities indicative of acute and sub ischemic strokes***
- ***Hemorrhagic & posterior reversible encephalopathy syndromes (PRES) related brain lesions in non-survivors of COVID-19 that might be triggered by virus induced endothelial disturbances***

TREATMENT

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Not Hospitalized, Mild to Moderate COVID-19	For patients who are not at high risk for disease progression, provide supportive care and symptomatic management **(AIII)**. For patients who are at high risk of disease progression (as defined by the FDA EUA criteria for treatment with anti-SARS-CoV-2 monoclonal antibodies), use one of the following combinations: • **Bamlanivimab plus etesevimab (AIIa)** • **Casirivimab plus imdevimab (AIIa)**
Hospitalized but Does Not Require Supplemental Oxygen	There are insufficient data to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, the use of remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use one of the following options: • **Remdesivir**[a,b] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone**[c] **plus remdesivir**[a,b] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)**[d,e] • **Dexamethasone**[c] (e.g., when combination therapy with remdesivir cannot be used or is not available) **(BI)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone**[c] **(AI)**[e] • **Dexamethasone**[c] **plus remdesivir**[a,b] **(BIII)**[d,e] For patients who were recently hospitalized[f] with rapidly increasing oxygen needs and systemic inflammation: • Add **tocilizumab**[g] to one of the two options above **(BIIa)**
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	• **Dexamethasone**[c] **(AI)**[h] For patients who are within 24 hours of admission to the ICU: • **Dexamethasone**[c] **plus tocilizumab**[g] **(BIIa)**

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of

TREATMENT OF NEUROLOGICAL MANIFESTATIONS OF COVID-19

- ***The Treatment of Neuro psychiatric Manifestations of COVID-19 is Tailor made depending upon the underlying pathology and clinical spectrum .***

- ***A solid basis for specific therapeutic measures does not yet exist .***

TREATMENT OF NEUROLOGICAL MANIFESTATIONS OF COVID-19

- *The treatment protocol is followed depending up on whether the manifestations are secondary to*

- *Immune mediated Demyelination*
- *Large or small vessel Ischemic or Haemorrhagic manifestations like Strokes both ischemic and Haemorrhagic*
- *Neuro inflammatory(infectious) complications like Meningitis / meningoencephalitis*
- *Autoimmune Inflammatory diseases like GBS , ADEM*
- *Chemosensory distrubances like Anosmia , Ageusia.*
- *Neurodegeneration*
- *Neurological manifestations secondary to Metabolic or Cortical involvement like Seizures , delirium .*

- ***HIGH DOSE METHYLPREDNISONE THERAPY** (1g/day) over 3-5 days can be considered in Infectious or Inflammatory conditions like Encephalitis & Meningitis*
- *For **AUTOIMMUNE INFLAMMATORY CONDITIONS like ADEM** , high dose **intravenous Corticosteroids with or without tapering can be considered followed by Intravenous Immunoglobulin therapy (0.4g/kg)** in cases of insufficient steroid response .*
- *IV Immunoglobulins and Plasma Exchange is considered equivalent in GBS .*
- *For Cranial Neuropathies High dose Corticosteroids are beneficial .*

- ***In Patients with Acute Ischemic Stroke , treatment with intravenous thrombolysis or thrombectomy if indicated should be considered .***

- ***Acute treatment of severe stroke must be carried out without interruption under protective measures including thrombectomy with cooperation of neurologists, interventional neuroradiologists, anesthetists and nurses with strict precautions due to the proximity to the patient and the risk of aerosol spread.***

- ***The decision whether patients should be treated on a neurological stroke unit or on a ward designed for the care of patients with COVID-19 with appropriate monitoring facilities must be made on a case-by-case basis, depending on the hospital's conditions .***

- ***Routine treatment with Anticoagulants , antiplatelets and anti-edema measures should be given for stroke patients.***

- *The therapy for inflammatory/autoimmune-associated diseases of the musculature, the neuromuscular junction, and the peripheral nerve should follow the current guidelines, including therapeutic measures such as plasmapheresis and immunoglobulins.*

- *Symptomatic treatment (e. g. pyridostigmine and 3,4-diaminopyridine) and immunomodulatory therapy (eculizumab) may be continued in consideration of the individual benefit-risk profile.*

- *For acute symptomatic seizures and status epilepticus, antiepileptic therapy is carried out according to the two relevant guidelines.*

COVID VACCINE ISSUES

- *The most efficient solution to end this pandemic is a safe and efficient vaccine. Classic platforms are used to develop vaccines including live-attenuated vaccine, inactivated vaccine, protein subunit vaccine, and viral vector.*

- *Nucleic acid vaccine uses next-generation platforms for their development.*

- *Cases of demyelinating disease were reported in the viral vector vaccine. Fever was one of the most frequent effects on all platforms, particularly in the mRNA platform. It could lower the seizure threshold, as the international league against epilepsy warns.*

TAKE HOME MESSAGE

- ***Neurological manifestations in 3-30% among COVID-19 patients***
- ***40-60% may not have systemic or respiratory symptoms of COVID-19***

- ***Stroke , GBS are common***
- ***Clinical features are usually similar but multiple pathophysiological mechanisms play in the etiological basis .***

- ***Treatment consists of dual management : treat the neurological disorder and treat the underlying COVID-19 infection.***
- ***Interactions have to be looked for in few situations***

THANK YOU


COVID-19
PREVENTION
WASH YOUR HANDS
FREQUENTLY
COVID-19
PREVENTION
KEEP DISTANCE
FROM OTHERS
1 M
COVID-19
PREVENTION
AVOID TOUCHING
EYES, NOSE & MOUTH.
COVID-19
PREVENTION
USE FACE MASK
COVID-19
PREVENTION
STAY HOME
IF YOU FEEL UNWELL
NEWS
COVID-19
PREVENTION
STAY INFORMED
AND FOLLOW ADVICE