Knowledge Update

COVID–19 : Virology, Immunopathogenesis and Neurological Manifestations

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The novel coronavirus SARS-Cov-2 has claimed the lives of thousands of unfortunate patients in this global pandemic and has infected millions throughout the globe. This pathogen has transgressed all international boundaries and overwhelmed all health systems in both developed and resource limited health setups. The COVID-19 illness has exposed deficits in research and development in respect to novel pathogens, healthcare funding and structure, people's personal health habits and practices and aspects of lifestyle and human behaviour. This current global crisis has exposed the vulnerability of the human race despite all the developments in the health sector and other human endeavours we are so proud and potentially complacent of. The virology features of this novel pathogen and the way it interacts with the human immune system and the responses that it generates has been a steep learning curve for all. The Neurology of COVID-19 has been protean and we are still learning every day from our patients. The need to organise randomised clinical trials for evidence based therapy has again been reemphasised to save lives and avoid iatrogenic errors and adverse patient outcome. Lives and livelihood for patients and health care providers has been severely threatened in this pandemic. But we must win.

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Key words **: COVID-19 SARS-Cov-2, Neurology, CSF, RT-PCR, MERS, Immunopathogenesis.**

SARS-COV-2 the infamous novel coronavirus and the COVID-19 illness that it causes was first diagnosed on December 8, 2019 in Wuhan, central China[1] after which it rapidly spread all over the world for the World Health Organisation (WHO) to declare it as a pandemic on 30 January 2020. Till date the Johns Hopkins database[2] shows 6,54,103 dead and 164,82,592 infected. The silver lining in the dark cloud is the recovery number of 95,90,529 individuals. We Indians presently occupy the unenviable position of being third among the total number of confirmed cases (1480) in the world and most alarmingly the sixth position in the number of deaths that of today has crossed the 33,000 mark[3]. As repeatedly locked downs are re-imposed and new hotspots are identified in India and globally, we continue to hold our breath in great anxiety and fear of life and livelihood. We remain alert in anticipation for the second wave[4] and for the lives at risk and the future and long-term ravages on the population and global economy through the novel virus.

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Editor's Comment :

- **We have all been exposed in regards to our knowledge base in being able to protect humanity against the unknown natural and novel pathogens with whom we cohabit this planet.**
- **The witnessed impact of a pandemic on global economy and livelihood should prioritise future health policy planning and further resource allocation to epidemiology and medical research and focus on population positive health initiatives.**
- **It is hoped the global community will work cooperatively and collaboratively under the auspices and leadership of the World Health Organisation to promote global health endeavours and be able to predict and manage any future threats to international health better to protect humanity.**

Virology :

SARS-CoV occurred in China in 2003[5] affecting approximately 8000 people with a 10% mortality rate and the Middle East respiratory syndrome (MERS) outbreak in Saudi Arabia in 2012[6] affecting 2500 individuals with a 35% mortality rate have been harbingers of the current corona virus as it has approximately 80% sequence homology with SARS-CoV. Peculiarly there is a 96% homology with a bat coronavirus and 92% with the pangolin coronavirus raising the hypothesis that it arose in animal species and then spread between the animals to infect humans[7]. The full sequence of SARS-CoV-2 to was published on 7 January 2020 confirming that this was

a beta coronavirus similar to other human coronaviruses responsible for 15% of all cases of acute viral nasopharyngitis("common cold"). The contagiousness of this coronavirus has made it immensely threatening to the human species as the polybasic cleavage site in the spike protein is a potential determinant of increased transmissibility. This protein helps the virus binds to the angiotensin converting enzyme 2(ACE2) receptor that is also a receptor for SARS-Cov-2[8]. This is followed by proteolytic cleavage of the spike protein by the transmembrane protease (TMPRSS2)[9]. The ACE2 is expressed abundantly in the lung alveolar cells which causes the primary respiratory presentation although is present in the brain, gut, kidney, gallbladder, testes and adrenal glands enabling the virus the opportunity to become a systemic illness. This contagiousness has given rise to the R_0 value[10] which indicates the number of people who can be infected by single individual to be as high as 4.7 – 6.6 leading to the number of infected individuals during the early epidemic stage doubling every 2.4 days.

In the preceding MERS and SARS epidemics the experience with neurological manifestations was limited as the total number of cases was approximately 10,500 and the complications were limited. However, with COVID-19 as the numbers affected are so much more, we are observing a broader spectrum of neurological manifestations and the long-term manifestations of the same will also be of interest with longitudinal follow up of recovered individuals and any long term sequalae.

Immunopathogenesis :

Asymptomatic or minor symptomatic SARS-CoV-2 infection occurs in approximately 80% individuals (mostly children and young adults). 20% develop varying degrees of severity of manifestations of COVID-19. SARS-CoV suppresses type I IFN response and downstream signalling molecules, and this dampening relates to disease severity[11]. SARS-CoV and SARS-CoV-2 use similar strategies to evade the innate immune response which the host precisely calibrates to control viral replication without triggering immune pathogenic injury. Mouse model studies in SARS showed rapid SARS-CoVreplication and delay in IFN-1 signalling leading to monocyte-macrophage accumulation, elevated lung cytokine and chemokine levels and associated vascular leakage and pneumonia. The resulting "cytokine storm" decreased the T cell countspreventing T cell response to SARS-CoV infection[12]. Similarly, in COVID-19 through significant reduction of the T cell subtypes (CD4 + and CD8+) and rise of serum IL-6, IL-10 and TNF alpha led to adverse ITU outcome. Reduced and delayed IFN-gamma production in the lungs potentiated viral injury through inadequate control of viral replication and up-regulation of above-mentioned inflammatory cytokines. This raises the hypothesis that immune dysregulation pathways rather than direct viral infection in the lung bed triggers cell injury and similar mechanisms may occur in the central nervous system. IL-6 production from infected neurons of transgenic mouse models of SARS-Cov is seen. Lymphopenia secondary to high circulating cytokines levels is seen.

T cell apoptosis by interaction with its receptor TNFR1 is a mechanism through which TNF alpha and IL-10 preventing T-cell proliferation and causing T cell exhaustion (high levels of PD-1 and Tim-3 exhaustion markers on the T cells) considerably weakens the T cell inflammatory response of SARS-CoV-2 in severe cases. Macrophage activation syndrome in addition blunts the adaptive immune response[13]. Clinically the high levels of circulating pro-inflammatory cytokines are hypothesised to cause confusion and alter consciousness.

A weakened T cell response would be unable to eliminate virus infected cerebral tissue and cause neurological dysfunction. To better understand the COVID-19 immunopathogenesis CSF cytokine profile, T cell response to SARS-Cov-2 and autopsy of CNS, PNS and muscle tissues are needed. A clear understanding will help guide therapy with IL-6 inhibitors[14] and evaluate/contraindicate corticosteroids that dampen the adaptive cellular immune response. All this will need to be staged to the specific immunological stage and state of the host immune response to the virus. We are not used to dealing with viruses in this manner in an acute setting by studying the individual immune profiles of patients in a clinical setting that determines the therapeutic approach as we analyse the immune system better on ITU patients.

Neurological manifestations of COVID 19 :

(A) Neuro invasion by SARS-CoV-2 —

Definitive evidence to support direct viral invasion of the brain includes positive CSF RT-PCR for SARS-Cov-2, demonstration of intrathecal synthesis of SARS-CoV-2 to specific antibodies or detection of SARS-CoV-2 antigen or RNA in brain tissue at biopsy or autopsy.

Cases meeting strict criteria as above for direct invasion of the virus into the CNS are rare although several plausible case reports are emergent[15-17]. In these, the CSF RT-PCR was positive while in others there were inflammatory features consistent with encephalitis on CSF and imaging but no evidence of

direct viral CNS invasion. In others presenting with "akinetic mutism" with nuchal rigidity the PCR was repeatedly negative. There are other case reports of patients with neuropsychiatric symptoms who had detectable NMDA receptor antibodies raising the possibility that SARS-Cov-2 may trigger an autoimmune encephalitis.

The repeated absence of CSF RT-PCR positivity (absence of direct viral invasion) brings in the scope of detection of intrathecal SARS-CoV-2 antibody synthesis or of viral antigen or nucleic acid in brain tissue, which may establish the evidence for viral invasion when the CSF RT-PCR studies are negative.

At post-mortem,the SARS-CoV antigen was detected in brain tissue by immunohistochemistry (IHC) and viral RNA by in situ hybridisation (ISH). Detection of intrathecal antibody synthesisis more sensitive than CSF nucleic acid synthesis for both West Nile virus neuroinvasive disease and enterovirus (EV) – D68 associated with acute flaccid myelitis, this paradigm would increase the diagnostic criteria of direct viral invasion. In EV D68, the site of sample collection from nasopharynx and throat gives early positivity at disease onset while correspondingly the CSF RT-PCR is positive only in a small minority. The sensitivity of nasopharyngeal RT-PCR ishigh and we need more CSF data to evaluate sensitivity of same in CSF.

(B) Post infectious and immune-mediated complications —

Associations of COVID-19 and GBS and GBS variants including Miller Fisher syndrome with characteristic electrophysiology, clinical features, MRI showing caudal nerve root enhancement with characteristic CSF findings in keeping with the diagnosis have been confirmed. The presentations started 5-10 days following COVID-19 symptom onset in this group of five patients with GBS. None of the patients had SARS-CoV-2 in CSF by RT-PCR[18]. Cases of acute necrotising encephalopathy (ANE) with positive nasopharyngeal RT-PCR and characteristic imaging findings raised the diagnostic possibility and causation[19]. Rare cases of ADEM with positive nasopharyngeal RT-PCR and characteristic brain imaging findings have been diagnosed. There are further case reports of acute flaccid myelitis as well.

An autopsy study undertaken on one ADEM subject did not show presence of the virus but otherwise classical pathology of acute haemorrhagic leukoencephalitis[20]. The rarity of post COVID-19 possible immune-mediated cases apart from GBS makes the diagnosis less certain. Also, the distinguishing point of ADEM with acute encephalopathy or encephalitis has made diagnostic certainty less firm. The CSF changes and absence of CSF RT-PCR has led to discussions of alternative aetiology, pathogenesis from COVID -19 infection or cooccurrence as explanations of the presenting symptoms. The cases have also been rapidly worked up and often incompletely investigated through resource limitation/restriction in COVID-19 times leading to diagnostic ambivalences.

(C) other COVID-19 related neurological disorders —

Loss or disturbance of smell and/or taste are well identified symptoms of COVID-19 19 infection. A detailed study from the Wuhan series of 31 patients showed 81% of COVID-19 cases showing smell disorder (46% anosmia, 29% hyposmia and 6% dysosmia) and disorders of taste in 94% (ageusia 45%, hypogeusia 23% and dysgeusia26%); the duration of these was 7.1days[21]. These findings were reproduced in a multicentre European study where recovery was within eight days.

In transgenic mice expressing the human SARS virus receptor (ACE2) and infected with SARS-Cov there is evidence that the virus enters the CNS through the nasopharyngeal route or infects the cardiorespiratory centre in medulla via the oropharyngeal route. Such evidence of host entry via this pathway has not been confirmed in humans. In some case reports MRI evidence of olfactory bulb contrast enhancement with subsequent normalisation raises this as a distinct possibility. Skeletal muscle injury manifesting as symptoms of muscle pain and raised CK was seen in severe COVID 19 patients and again through inadequate clinical and laboratory workup it is difficult to be certain on these aspects to any further extent of causation.

(D) Neurological complications of systemic COVID-19 —

Initial reports suggested that 36% of patients in Wuhan China had neurological symptoms. The non-localising symptoms were ones of dizziness, headache, impaired consciousness, acute strokes, ataxia and seizures. It was also noted that patients with severe pneumonia had higher incidence of CNS disease. Impairment of consciousness was common particularly among the cohort of older (58 ±15 yrs.) versus younger (49± 15yrs) subjects and in patients with commodities including hypertension, diabetes, cancers, cardiac, previous strokes or kidney disease (48% vs 33%; p=0.03). This group also had evidence of systemic inflammation – elevated CRP, D dimer and evidence of hepatic and renal dysfunction. MRI studies

showed evidence of cerebral perfusion disturbances and RT-PCR for SARS-Cov-2 negative in the CSF. In a specific study of five patients with the ARDS and delayed recovery following mechanical ventilation, MRI studies showed enhancement of the wall of the basal brain arteries without enlargement of the vessel wall or stenosis. CSF RT-PCR was negative and treatment with methylprednisolone resulted in marked improvement after 48 to 72 hours. The hypothesis of an endothelialitis rather than vasculitis responsible for the encephalopathy was thus proposed, resulting from direct infection of the endothelial cells by SARS-CoV-2. There was associated endothelial inflammation at post-mortem in a variety of organs which however did not include the brain[22].

In the brain autopsy studies microthrombi, acute infarction, focal parenchymal infiltrates of T lymphocytes, minimal inflammation and slight neuronal loss and no acute hypoxemic ischaemic changes were seen. ACE2 was expressed in the brain capillaries. There was systemic inflammation in all these patients. The second major manifestation of systemic COVID-19 is acute cerebrovascular disease. These occurred between 8 and 24 days after onset of COVID-19. The patients had a highly prothrombotic state with exceedingly high D dimer levels, elevated ferritin, detectable lupus anticoagulant, anticardiolipin IgA, antiphospholipid IgA and IgM against B2-glycoprotein-1 in varying combinations.

In older patients the ischaemic involvement of predominant large vessels was resultant from the systemic hyperinflammatory state whereas in younger subjects hypercoagulability was causative.

Paediatric patients presenting with the Kawasaki disease like multisystem inflammatory syndrome (MIS) have also been described[23].

Thus SARS-CoV-2 infects and injures endothelial cells. It is not definitive if this then leads to a vasculopathy through virus induced injury to endothelium or true vasculitis is the main driver of COVID-19 cerebrovascular syndromes.

Detailed vessel wall imaging and neuropathological analysis will help to distinguish.

This will have impact on the role of antiplatelet or anticoagulant drugs dependent on the underlying pathophysiological mechanism in each patient. The recommendations for immunomodulatory therapies dependent upon the dysfunction of specific arms of the immune system – cytokines, interleukins,and other immune active substances from monocyte/macrophages and T cells at the specific stage of the COVID-19 illness dependent on close immunological monitoring in each case with associated comorbidities will need to be trial driven and evidence based[24]. This has been based on key opinion leader opinion based to serve the best interest of the critically ill patient so far. Hence, the plethora of drugs being recommended so far and possibility of harm if careful selection of pharmacological intervention is not matched to the specific immune dysfunction in the specific patient – "personalised medicine"

COVID-19 has tested us as clinicians who have had to respond expeditiously to save lives of millions globally using the wealth of their experience collaboratively globally including using the social media (Twitter, FB etc) to provide expert opinion on published papers and therapies. Now is the time to design effective trials of therapies to have evidence-based medicine in place and to research virology and immunology[25]. We also need to follow up the COVID-19 patients longitudinally and to investigate them in a structured manner to get the best clinical information from the ravages of a novel virus of apocalyptic-proportions that nearly brought us to the cliff edge – we surely will win this cliff hanger with global collaboration in research and health care delivery and strategy planning with WHO and National Health Departments.

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COVID-19: A Global Threat to the Nervous System

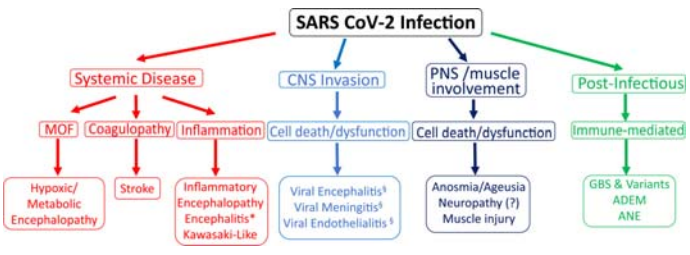

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FIGURE: Mechanisms of severe acute respiratory syndrome-coronavirus type 2 (SARS-CoV-2) neuropathogenesis. SARS-CoV-2 pathogenic effects on the nervous system are likely multifactorial, including manifestations of systemic disease, direct neuro-invasion of the central nervous system (CNS), involvement of the peripheral nervous system (PNS) and muscle, as well as through a postinfectious, immune-mediated mechanism. MOF = multi-organ failure; GBS = Guillain-Barre syndrome. *CNS inflammation (CSF pleocytosis and proteinorrachia) with no evidence of direct viral infection of CNS; §direct evidence of viral invasion (reverse transcriptase-polymerase chain reaction positive [RT-PCR+], biopsy); ADEM = acute disseminated encephalomyelitis; ANE = acute necrotizing encephalopathy. [Color figure can be viewed at www.annalsofneurology.org]

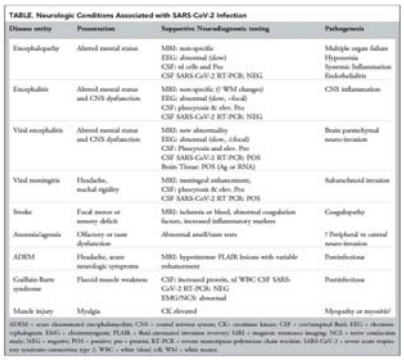

TABLE. Neurologic Conditions Associated with SARS-CoV-2 Infection

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

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

Table 1: Neurologically-notable coronaviruses in humans and animals[ref 6-10]

Coronavirus	Host	Host Entry	Reservoir	Site of discovery	Major Geographic Distribution	Systemic Features	Associated Neurological Features
SARS-CoV	Human	ACE2	Bats, civets	China	China, Taiwan, Singapore, Vietnam	Mild to severe respiratory illness	Encephalopathy, seizure, [illegible] polyneuropathy, myopathy
MERS-CoV (50% identity with SARS-CoV-2)[ref 11-13]	Human	DPP4	Bats, camels	Saudi Arabia	Egypt, Oman, Qatar, Saudi Arabia	Moderate to severe respiratory illness	Encephalopathy, ischemic stroke, intracerebral hemorrhage
HCoV-OC43	Human	Unknown	Bats, rodents	[illegible]	[illegible]	Mild respiratory illness	ADEM (case report), acute encephalitis (possible)
HCoV-229E	Human	APN	Bats, camelids	Global	Global	Mild respiratory illness	Encephalitis (possible)
HCoV-NL63[ref 14,15]	Human	ACE2	[illegible]	Global	Global	Mild respiratory illness	None reported
Mouse hepatitis virus	Mouse	[illegible]	[illegible]	[illegible]	[illegible]	Severe pneumonitis, SARS	Acute encephalitis or chronic demyelinating disease[ref 16,17]
Rabdomyosarcoma coronavirus	Rat	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Neurologic infection[ref 18,19]
Hemagglutinating encephalomyocarditis virus	Pig	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Neurologic infection[ref 20,21]

ACE2 = angiotensin converting enzyme 2, APN = aminopeptidase N, DPP4 = dipeptidyl peptidase 4

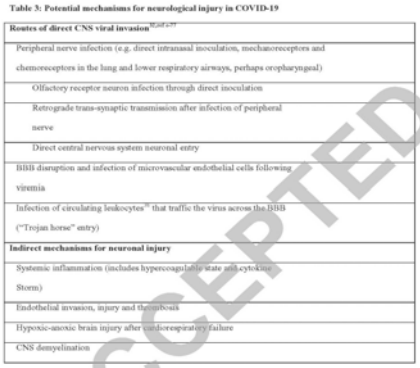

Table 3: Potential mechanisms for neurological injury in COVID-19

Routes of direct CNS viral invasion[ref 22,23,24]
Peripheral nerve infection (e.g. direct intranasal inoculation, mechanoreceptors and chemoreceptors in the lung and lower respiratory airways, perhaps oropharyngeal)
Olfactory receptor neuron infection through direct inoculation
Retrograde trans-synaptic transmission after infection of peripheral nerve
Direct central nervous system neuronal entry
BBB disruption and infection of microvascular endothelial cells following viremia
Infection of circulating leukocytes[ref 25] that traffic the virus across the BBB ("Trojan horse" entry)
Indirect mechanisms for neuronal injury
Systemic inflammation (includes hypercoagulable state and cytokine Storm)
Endothelial invasion, injury and thrombosis
Hypoxic-anoxic brain injury after cardiorespiratory failure
CNS demyelination

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