NEURO COVID

INTRODUCTION

In the present pandemic of Corona since 2020, it has been seen that the virus SAARS CoV2 affects almost all systems of the body.

Neurological system is no exception and it has been seen in my experience that the entire neuro-axis may get affected. It was suggested that neurological symptoms are more common in patients with severe disease.

These may be related to the tremendous immune storm that happens in the disease.

The exact mechanism of entry into the central nervous system (CNS) is unknown, but currently discussed routes include retrograde neuronal transport across infected neurons, entry via the olfactory nerve, infection of the vascular endothelium, or white blood cell migration across the blood-brain barrier.

One possible method of direct nervous system entry is via angiotensin-converting enzyme-2 (ACE2). SARS-Cov-2 attaches to this ACE2, which is most frequently found in the *lungs but is also present on neurons and glial cells in the central nervous system.*

Surprisingly, a subspecies of the corona virus family is called Middle East Respiratory Syndrome (MERS) which has also been implicated in neurological manifestations in rare cases. There have only been three documented cases of neuropathy in MERS.

CENTRAL NERVOUS SYSTEM MANIFESTATIONS

1**] MENINGES**

Covid can cause sudden deterioration in power of limbs or facial muscles (cranial nerves) or a sudden higher requirement of Oxygen. Clinical examination may show only motor involvement, paring bladder & bowel and the sensory systems. It can come in an ascending as well as descending way.

The electrophysiology will show variants of Gullain barre and a CSF study will show the typical albuminocytological dissociation.

CSF RT-PCR FOR COVID-19 WAS NEGATIVE IN ALL PATIENTS.

In descending variant, there may be nerve sparing, but ophthalmoplegia and ataxia may be seen.(Miller Fischer variant). Whatever it is, the response to IVIG is usually good although at occasions t may fail too.

The cases with who presented with anosmia, ageusia, right internuclear ophthalmoparesis, right fascicular oculomotor palsy, ataxia, areflexia, albuminocytologic dissociation, and positive testing for GD1b-IgG antibodies,ee more seen to be ssociated with AIDP.

2] **BRAIN**

Non specific symptoms

The neurological symptoms reported were headache (6%), vertigo (3.4%), numbness/paresthesia (3.1%), altered consciousness (2%), hyposmia / anosmia (1.4%) as well as loss of taste.

The olfactory dysfunction appeared before, in unison, and after the appearance of general symptoms in majority of patients or the onset of the olfactory dysfunction occurred at the same time or immediately after the onset of their other COVID-19 symptoms.

Once in the brain, they have the potential to spread to the thalamus and brain stem, two regions highly involved in coronaviridae infections.

Zinc deficiency can lead to cytokine production as well as olfactory and gustatory impairments.

Diffuse myalgia, depressive symptoms, fatgue and disturbed sleep are also complained after recovery. A diagnosis of vitamin B6 includes manifestations such as weakness, paresthesia, and confusion and may be tried in post Covid patients with such symptoms.

Headache

Eight retrospective studies reported COVID-19 patients presenting with headache. An overall average of 19.88% of patients experienced headache.

Encephalopathy

CT and magnetic resonance imaging (MRI) of the brain were unremarkable. Electroencephalogram (EEG) was employed in the USA and Italy case which revealed diffuse slowing consistent with encephalopathy.

Chloroquine, lopinavir, and ritonavir were administered in the first two cases. At the time of the report, the first patient was critically ill and the second had complete resolution of her symptoms. Certain patients showed dramatic response to high-dose steroids.

Ischemic stroke

Laboratory studies showed elevated D-dimer, decreased fibrinogen level, prolonged prothrombin time (PT), and activated partial thromboplastin time (APTT). Additionally, serum cytokine levels including IL-6, IL-8, and IL-10, were markedly elevated.

Ferritin elvation has been demonstrated and the role of Iron chelation demonstrated in some studies.

Massive obstructions in major arteies has been reported with large areas of brain damage.

Intracerebral hemorrhage

Also reported is Haemorragic stroke. Its association is common in males, cigarette smokers, elevated BP. Low platelets is also a reason. Haemorages should hence be anticipated in patients with such profile and Covids complainining of sudden headaches should always have imaging to rule out all forms of intracerebral haemorrhages.

Encephalitis and encephalomyelitis

Ages range from early 20s to late 60s. All of them had preceding symptoms of fever and cough followed by a rapidly deteriorating level of consciousness.

Meningeal irritability in the form of nuchal rigidity, Kernig's, and Brudzinski's if present has worse prognosis as well as patients presenting with psychosis.

Other than ordinary infective encephalitis, immune encephalitis is common as well.

Other infections

Recently there was a spurt of mucor in Covid patients. Mucor can occur in any immune-compromised person, but in Covids a peculiar thing was observed.

In2 of my patients (both referred from outside) one had to sacrifice only the eye (Amphocil started before black colour developed, on my clinical suspicion) whereas the other had to sacrifice the eye with a part of frontal lobe of brain (Referred to me late).

On reviewing, I found that both were treated with oxygen from cylinders with connectors using tap, instead of distilled water (NB; we have our own Oxygen plant and do not require cylinders usually).

This explains probably the virulence of mucor or black Fungus in Covids in the mask area instead of generalised as in HIV.

Seizures

In those with focal or status epilepticus, an EEG may show abundant bursts of anterior low-medium voltage irregular spike and waves superimposed on an irregularly slowed theta background.

Follow-up MRI brain which revealed hemorrhagic, rim-enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions.

Treatment of the encephalitis along with simultaneous therapy (whatever regime) for covid is required to control seizure unlike non-covid status.

Cranial neuropathy

Bell's palsy

There was no preceding fever, cough, or respiratory symptoms. Physical examination showed a lower motor neuron facial nerve paralysis. *MRI brain showed no abnormality*.

However, a throat swab RT-PCR turned positive for SARS-CoV-2 virus and the CT chest revealed ground-glass shadows in the right lower lung.

Point of importance is in such patients' treatment with Steroids are Acyclovir is not enough as in non-covid Bell's.

They may need antiviral treatment with umifenovir and ribavirin along with.

Other cranial nerves are rarely reported but more so after vaccination.

3] **SPINE**

Acute myelitis

Patients of Covid with rapidly progressing flaccid lower extremity paralysis and paresthesia and numbness below T10 were observed. Planters were down going bilaterally (initial shock stage), later up going seen.

Clinically myelitis may present post Covid as well. *Copper deficiency can result in myelopathy.*

Treatment with ganciclovir, lopinavir/ritonavir, moxifloxacin, dexamethasone, IVIG, and mecobalamin may be required.Improvemnt in power has been documented though complete recovery of sensory, motor or bladder may require more time than normal non covids.

4] **PERIPHERAL NERVOUS SYSTEM MANIFESTATIONS**

Many times this entity of PNS involvement goes unnoticed. It comes in notice when either the patient develops weakness of limbs, which may not be complete so to suspect neuropathy, or it may present s difficulty in extubation or seen fluctuations in BP. (Autonomic involvement). In such cases a thorough clinical examination should be done followed by Electrophysiological study.

Magnetic resonance imaging of the brain and spine, spinal fluid analysis, serum studies including creatinine kinase and C-reactive protein should be done to rule out spinal or other causes of weakness. A high CPK may indicate myopathy as well.

Elevated lactate dehydrogenase, low serum copper (72.9 (ref: 80.0-155.0 ug/dL)) and low vitamin B6 (14.6 (ref: 20.0-125.0 nmol/L)) may be indicative too.

Empiric treatment with intravenous steroids (1000 mg methylprednisolone for three days), followed by a total of 2 g/kg of intravenous immunoglobulin (IVIG) is given over five days. Pain management was done with gabapentin and ketorolac. (There are no clinical studies on the use of gabapentin for SARS-Cov-2-related neuropathic pain, but they are traditionally used in neuropathic pain, in general).

Copper and vitamin B6 supplementation is necessary. Although Copper deficiency can result in myelopathy but not peripheral neuropathy, it has shown improvement.

Reported improvement is closer to baseline, but residual, exertional, and mild bilateral lower extremity pain, numbness, and weakness may persist.

Awareness and early treatment of peripheral neuropathy in SARS-Cov-2 can result in improved clinical outcomes for patients.

An entity of Subacute peripheral neuropathy has been rarely reported.

5] **Myalgia and myositis**

An overall average of 25.1% of patients reported experiencing myalgia in seven retrospective studies ((rhabdomyolysis).

Compared with the patients without muscle injury, patients with muscle injury had significantly higher levels of creatine kinase (median 400 U/L [range 203.0 to 12,216.0] versus median 58.5 U/L [range 8.8–212]; $P < 0.001$).

In addition, patients with muscle injury had higher C-reactive protein (CRP) levels and D-dimer levels—manifestations of increased inflammatory response and associated coagulopathy.

Furthermore, patients with muscle injury showed more signs of multi-organ damage, including more serious liver and kidney abnormalities, than patients without muscle injury.

SUMMARY

It is common knowledge that post-viral syndrome refers to a sense of fatigue one gets for weeks to months after fighting off a viral infection. One research study described the potential of a post COVID-19 syndrome following SARS-Cov-2 including symptoms such as chronic fatigue, diffuse myalgia, depressive symptoms, and disturbed sleep due to neuroimmune exhaustion.

Post-viral syndrome can take three courses:

- Complete recovery,
- Relapsing and remitting course due to stressors,
- Or chronic symptoms.

Of note, hydroxychloroquine often used for SARS-Cov-2 can cause adverse neurological side effects such as peripheral neuropathy, myopathy, irritability, and psychosis, so should be used cautiously if neurological symptoms may be present.

COVID-19 can also present with central nervous system manifestations such as ischemic stroke, intracerebral hemorrhage, encephalo-myelitis, and acute myelitis, peripheral nervous manifestations such as Guillain-Barré syndrome and Bell's palsy, and skeletal muscle Neuropathy could also be caused by the host's immune response reacting to the viral infection. It may be possible for SARS-Cov-2 to cause a cytokine storm, characterized by the immune system's response to SARS-Cov-2 by rapidly releasing cytokines.

This can result in respiratory failure and neurological symptoms.

How the virus enters the central nervous system is still a subject of debate. One plausible route of entry is through the olfactory nerve. Retrograde transfer into the axon, whether through synapses, endocytosis, or exocytosis, could explain viral migration into the brain

Not much proof for entry through nasal mucosa has yet been documented.

Another theory suggests if SARS-CoV-2 gained access to the general circulation, it could potentially invade the cerebral circulation and continue viral spread. Slow movement in the cerebral microvasculature may promote interaction of the SARS-CoV-2 S protein and capillary endothelium ACE2 receptor. Once bound, the virus would have the potential to

infect, damage, and bud from the capillary endothelium, thereby facilitating viral entry into the cerebrum.

Viruses do not have to enter the brain to cause damage; they can activate an immune response that triggers subsequent damage within neuronal tissue. SARS-CoV-2 has been reported to cause a massive release of cytokines, a syndrome known as “cytokine storm”—downstream effects of this immune response include endothelial damage, disseminated intravascular coagulation, and disrupted cerebral auto-regulation.

Peri- and post-infectious hyposmia and hypogeusia is hypothesized to be secondary to olfactory nerve and/or apparatus damage from direct insult of viral infection

Future research is grounded by the hypothesis of molecular mimicry, where mimicry between microbial and nerve antigens is thought to be a major driving force behind the development of the disorder.