Pakistan Journal of Neurological Sciences (PJNS)

Volume 15 | Issue 1 Article 2

3-2020

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Date of submission: *April 22. 2020* ***Date of revision:*** *April 27,2020* ***Date of acceptance:*** *April 30,2020*

ABSTRACT

Severe acute respiratory syndrome corona virus 2 (SARS CoV 2) seems to display an increasing affinity for the nervous system. The ongoing pandemic has made evident that diverse neurological manifestations may occur with COVID 19. Headache and dizziness remain the most common symptoms however stroke, seizures, encephalopathy, neuropathy and skeletal muscle injury may be seen. An increasing number of patients report initial anosmia and ageusia.
Tendency for serious illness is believed to be in the elderly or people with a history of diabetes, high blood pressure and heart disease. Many patients on immunosuppressive therapies such as multiple sclerosis, myasthenia gravis or sarcoidosis are additionally high risk. Angiotensin-converting enzyme 2 (ACE 2) has been identified as the cellular receptor for SARS CoV 2 present in both neurons and glial tissue. The pathophysiology of neurotoxicity at best remains elusive with dysregulation of homeostasis and pro inflammatory cytokine production causing direct, indirect and post infectious neurological complications. Vigilant observation for neurological involvement is important not only to prevent spread of this highly contagious disease but also for appropriate, timely management. A directed neurological examination limiting exposure of medical personnel to potentially infected patients is mandatory. Appropriate constrained investigations should be considered only if there is a likelihood of changing management. Tele neurology consultations, whenever possible is the need of the hour. Outcomes of COVID 19 patients with severe illness and neurological complications remains grave. Pharmaceutical research needs to change directions to expedite the development of a possible vaccine and also accelerate in the quest for newer antiviral agents.

KEY WORDS: SARS-CoV2, COVID 19, ACE 2, Stroke , Seizures, neurological, meningitis

History of Corona Viruses:

Coronavirus disease was initially described in 1931, with the first coronavirus (HCoV-229E) isolated from humans in 1965. Until the outbreak of severe acute respiratory syndrome (SARS CoV) in Guangdong, China in 2002 only two human coronaviruses (HCoV) were known – HCoV-229E and HCoV-OC43. More than 8000 SARS CoV cases were reported to the World Health Organization (WHO) in 2002-03 and it caused approximately 800 deaths worldwide with disease identification in 29 countries, last case was seen in 2004. The Middle East respiratory syndrome associated coronavirus (MERS-CoV) was the next identified coronavirus in 2012 in Saudi Arabia. Larger outbreaks have occurred later in South Korea in 2015 and in Saudi Arabia in 2018.About 2,500 cases have been reported as of January 2020 from more than 26 countries causing approximately 900 deaths in total.
Viral genome analysis revealed that SARS-CoV belongs to Group B and MERS-CoV belongs to Group C beta coronavirus, respectively, and both are closely related to coronavirus strains found in bats.[1]
Intermediate mammalian hosts, such as civet cats, have been implicated for SARS CoV before its adaptation for human transmission, and evidence through virus or antibody detection suggests that the dromedary camels are likely the host for MERS-CoV.[2]
SARS-CoV-2 recently identified in Wuhan China in December 2019 is a strain of SARS-CoV and it shares the same receptor; angiotensin converting enzyme 2 (ACE2). It is believed to have zoonotic origins and has close genetic similarity to bat coronaviruses.[3]

Epidemiology of COVID 19 and Burden of disease:

The WHO was informed of 44 cases of pneumonia of unknown microbial etiology in Wuhan-Hubei China on 31 December 2019. Within a few weeks, the virus was

identified as SARS CoV 2. Most of the patients in the outbreak reported a link to the Huanan South China Seafood and live animal Market. Rapid spread occurred throughout China and within one month several other countries, including Italy, the United States and Germany. Since then, the outbreak has escalated rapidly, with the WHO first declaring this as a public health emergency of international concern on 30 January 2020 and then formally declaring it a pandemic on 11 March 2020. Difficulty controlling such an aggressive spread resulted partly due to the extensive size of Wuhan; Central China's transportation hub, which has a full-time population of more than 9 million and a transient population of an additional 5.10 million. In an attempt to reduce virus transmission, on January 23, 2020, authorities locked down Wuhan, but by that time approximately 5 million persons had already left.[4] The WHO COVID-19 Situation Report for April 21,2020 reports 2.4 million confirmed cases of COVID 19 and 162,956 deaths.[5] In Pakistan alone at the writing of this manuscript the affected number was approximately 10,513 with more than 224 mortalities. All provinces in Pakistan have been affected with the largest numbers from Punjab as per local authorities. The incoming numbers have an increasing trend either because of improved testing availability or because the peak of this pandemic in Pakistan has not been reached and the worst is yet to come.

Demographics and Transmission:

As an emerging acute respiratory infectious disease, COVID-19 primarily spreads through the respiratory tract. Transmission occurs primarily via respiratory droplets within a range of about 1.8 metres (6 ft). Indirect contact via contaminated surfaces is another possible cause of infection. The virus is inactivated by soap, which destabilizes its lipid bilayer. Based on current epidemiological investigation, the incubation period is 1–14 days, mostly 3–7 days. The pharynx reaches peak viral load approximately four days after infection and the COVID-19 is contagious during the latency period. It is highly transmissible in humans, especially in the elderly and people with underlying diseases like hypertension, ischemic heart disease and diabetes mellitus. Each infection from the virus is expected to result in 1.4 to 3.9 new infections when no members of the community are immune and no preventive measures are taken. Emerging evidence suggests that ambient temperature has no significant impact on the transmission of COVID-19; however, further research is required on how weather conditions influence transmission.[6] The median age of patients is 47–59 years, and 41.9–45.7% of patients are females.[7]

Data from the largest case series in China found that 87% of confirmed cases were aged 30 to 79 years, 1% were aged 9 years or younger, 1% were aged 10 to 19 years, and 3% were aged 80 years or older. Approximately 51% of patients were male and 49% were female.[8] In the US, older patients (aged ≥65 years) accounted for 31% of all cases, 45% of hospitalizations, 53% of intensive care unit admissions, and 80% of deaths, with the highest incidence of severe outcomes in patients aged ≥85 years.[9] Infection in children is reported much less commonly than amongst adults.

Pathophysiology:

SARS CoV2 is an enveloped, positive sense, single stranded RNA virus with a diameter of approximately 60-140 nanometers. The viral envelope consists of a lipid bilayer with four structural proteins known as S (spike (E (envelope), M (membrane) and N (nucleocapsid). Interaction between the spike protein and host cell receptor is essential for virulence and infectivity.[10] Following invasion of the lung epithelium, SARS-CoV directly infects T cells and macrophages, contributing to lymphopenia with reduced CD4+ and CD8+ cell counts and dysregulation of normal adaptive immune responses. Excessive production of pro-inflammatory cytokines including interleukins (IL-1, IL-6, IL-10), and tumor necrosis factor-alpha with subsequent downregulation of anti- inflammatory cytokines such as interferon gamma are thought to contribute to excessive inflammation and activation of pro-apoptotic pathway.[11] In some cases, adaptive immune responses might become directed against host epitopes, resulting in post-infectious autoimmune reactions that prolong the inflammatory phase and induce tissue destruction even after the virus has been cleared.

Mechanisms of Neuronal injury:

Angiotensin-converting enzyme 2 (ACE 2) is the cellular receptor for the new SARS-CoV-2 This is present in multiple human organs including the brain and glial tissue and thus this makes the central nervous system a potential target.[12] There may be direct infiltration of the CNS through the nasal epithelium and entrance into the olfactory pathway with the subsequent retrograde trans-synaptic spread. Hematogenous spread with secondary neurologic manifestations of COVID-19 are thought to be the result of widespread dysregulation of homeostasis and cytokine production with pulmonary, renal, hepatic, and cardiovascular injury.[13]. Besides coronavirus specific antibodies have been shown to activate macrophages resulting in their migration into the CNS and ultimately cause

demyelination. Infection with COVID 19 promotes atherosclerosis, inflammation and local thrombosis in the presence of systemic inflammation the resultant elevation in C reactive protein and D dimer increases the risk of acute cerebrovascular disease.[14] Molecular mimicry between specific viral proteins and proteins on peripheral nerves (gangliosides) leads to an innocent bystander attack against the myelin or axon, the most likely mechanism behind peripheral nerve injury. There is no current evidence of direct viral invasion with inflammation and degeneration of motor neurons and peripheral nerves as seen in some other viral infections like poliovirus, West Nile, Herpes Zoster, or Cytomegalovirus etc.

Neurological symptoms:

Neurological signs and symptoms fall into three main categories; central nervous symptoms (CNS), peripheral nervous symptoms (PNS) and skeletal muscular symptoms.3 These clinical features may be the presenting complaints or as more commonly seen arise during the more frequently seen respiratory and febrile illness. CNS manifestations most commonly seen include dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizures. PNS manifestations included taste impairment, smell impairment and nerve pain. Skeletal muscular injury manifestations include myalgias. In the largest study to date on 214 patients from Wuhan, China, overall, 78 patients (36.4%) had neurologic manifestations. 126 patients (58.9%) had non severe infection and 88 patients (41.1%) had severe infection according to their respiratory status. Patients with severe infection were more likely to develop neurologic manifestations, especially acute cerebrovascular disease [5.7%]; conscious disturbance [14.8%] and skeletal muscle injury [19.3%].3 Another recent report of 99 COVID-19 patients in Wuhan also described neurological complications with confusion (9%) and headache (8%) being most commonly seen.[15] Most neurologic manifestations occur early in the illness (median time, 1-2 days). Of 6 patients with acute cerebrovascular disease, 2 arrived at the emergency department owing to the sudden onset of hemiplegia but without any typical symptoms of fever, cough, anorexia, and diarrhea of COVID-19. Their lung lesions were found by an emergent lung CT and were diagnosed as having COVID-19 by a positive SARS-CoV-2 nucleic acid detection in the later stage.3 Loss of smell and taste may precede respiratory symptoms and suggest early neurological involvement. The American Academy of Otolaryngology recently proposed that anosmia, hyposmia, and dysgeusia should be added to the list of COVID-19 screening symptoms and urged precautionary isolation for individuals with these symptoms, even in the absence of respiratory disease.[16]

Neurological syndromes:

Isolated new cases of COVID 19 with neurological syndromes are emerging every day from all around the world. Ischemic strokes have been reported in 5% of patients with severe COVID -19 infections and in 1% of non-severe infections due to the COVID 19 from recent data considering the patients are in a pro thrombotic state.3 There was also one patient with spontaneous intra cerebral hemorrhage and cerebral venous sinus thrombosis each in the same study.

Encephalopathy and acute hemorrhagic necrotizing encephalopathy have recently been reported with COVID19 which are rare complications of influenza and other viral infections.[17] Myopathies, rhabdomyolysis, viral myositis, critical illness myopathy are all possibilities with COVID19. In recently published studies from China myalgia developed in up to 44% of hospitalized patients and elevated creatine kinase in up to 33%.[18] There is no proven direct causality with Guillain Barre Syndrome as seen in some other viruses like influenza, H1N1, ZIKA, EBV etc. however some new case reports exist.[19] Association with demyelination including Multiple sclerosis and Acute disseminated encephalomyelitis has been reported in the past.[20]

COVID-19 and Stroke

Acute strokes presenting in endemic areas in emergency department may need to be checked for COVID-19. The stroke team evaluating for patient should divide to conserve personal protective equipment and limit the potential for accidental exposure. Patients needing tissue plasminogen activator (tPA) during the one-hour infusion may be monitored every 15 minutes by a single stroke team member situated in the patient's room. In cases of mechanical thrombectomy, groin checks can be done by team members entering for other reasons every 4 hours after the initial monitoring in the intervention radiology suite.[21] Non-contrast head CTs with possible or confirmed COVID-19 should be reserved for patients with significant change in neurologic examination. Repeat imaging in neurologically stable patients who have not received IV tPA or mechanical thrombectomy should be avoided. Additional studies including MRI, Echocardiogram's and Doppler's should be considered only if likelihood of changing management. Even in patients without COVID-19, the

effectiveness of routine brain MRI to guide treatment selection is uncertain.[22]

COVID-19 and Seizures

Metabolic derangements may be common in SARS-CoV2 infected patients and these should be evaluated for possibly causing seizures. Severely affected have compromised renal and hepatic systems and appropriate antiseizure medication should be carefully selected. Brivaracetam, lacosamide, Levetiracetam, Zonisamide is advised with abnormal liver tests.[23]

COVID19 and Headache

Headache appears to be the most common neurological complaint with COVID-19. The putative role of ACE2 in the pathophysiology has recently fueled concerns regarding the use of non- steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, commonly used for headache. These are known to induce up-regulation of ACE2 and, in theory, may facilitate infection with COVID-19.[24] Sodium valproate should be avoided amid to concerns of liver injury.

COVID-19 and GBS

All patients with suspected or diagnosed COVID-19 with acute flaccid weakness should be admitted in intensive care units. Elective endotracheal intubation should be considered when single breath count test < 20, use of accessory muscles or paradoxical breathing and neck flexion weakness is noted. The generally considered CSF analysis for cytological dissociation, maybe warranted if it will change therapeutic decision as it may be normal in one third to one half in first week of symptoms. NCS 1-2 weeks after symptom onset should be considered. Intravenous immunoglobulins (IVIg) 2g/kg administered over 5 days is the standard of care. Plasmapheresis over 5 cycles is an equally efficacious alternative. Mild symptoms may not need treatment; decision should be weighed against lengthy hospital stay.[25] The role of high dose IVIg in a recent case series published with COVID-19, all of whom were successfully treated at the early stage of clinical deterioration with the resultant initiation of a randomized controlled trial.[26] This may lead us to rethink the equal efficacy that has been long established when treating patients with muscle or nerve involvement with plasma exchange versus IVIg. Serial PFTs (pulmonary function tests) at least q8h in first 24 hours. Daily vital sign, urine output, and last bowel movement charting should be maintained for anticipating autonomic dysfunction. [27]

Neuroimaging

Although the full spectrum of neuro-imaging findings in COVID 19 is still unknown. The risk of contamination remains high. A non-contrast CT Head to exclude acute stroke in patients with possible or confirmed COVID 19 should be reserved for times when actionable information is likely to be obtained, or when a significant change in the neurological examination is seen. A CT angiogram of the head and neck may be required in cases of subarachnoid hemorrhage. Additional studies including MRI with gadolinium may be required in patients with a history of seizures or unexplained encephalopathy. In one recently published study from Strasbourg, France, between March 3 and April 3, 2020 in patients with confirmed COVID 19 with encephalopathy. MRI Brain showed leptomeningeal enhancement predominately in occipital lobe in eight out of 13 patients. Small diffusion abnormalities indicating asymptomatic acute ischemic stroke were seen in two patients. Bilateral frontotemporal hypo-perfusion was noted in all 11 of these patients who underwent perfusion imaging.[28] Hemorrhagic ring enhancing lesions within the bilateral thalami and medial temporal lobes on MRI Brain has been described in a patient with acute hemorrhagic encephalopathy.[17]

Cerebrospinal fluid:

A cerebrospinal fluid (CSF) examination may be required to exclude possible causes of impaired consciousness. All standard tests to exclude CNS infections should be done simultaneously despite of suspected encephalitis and encephalopathy due to COVID-19. Cerebrospinal fluid is usually clear and colorless with mild pleocytosis and lymphocytic predominance. CSF oligoclonal bands may be present with an identical electrophoretic pattern in serum[28]. SARS-CoV-2 nucleocapsid protein genes can be detected by using PCR and is recommended in highly suspicious cases. In a recent case report with meningitis the opening pressure of CSF was increased up to 320 mmH2O. The CSF cell count was 12/μ L. 10 mononuclear and 2 polymorphonuclear cells without red blood cells were noted. Although the specific SARSCoV-2 RNA was not detected in the nasopharyngeal swab of this patient, it was detected in CSF.[29]

Electroencephalogram:

Electroencephalogram (EEG) may be needed in unexplained drowsiness or with uncontrolled seizures. Non-convulsive seizures seen in critically ill patients in up to 10% .[30] 24 hour monitoring maybe required in appropriate cases, ideally performed with disposable EEG leads. Seizures were observed with other types of coronavirus infections in up to 6 - 50% of affected

children.[31] The EEG findings although are non-specific may show diffuse or bifrontal slowing consistent with encephalopathy.[28]

Nerve conduction studies and electromyography:
Nerve conduction studies (NCS) and electromyography (EMG) may be necessary with patient acute flaccid paralysis or myositis. Reports of GBS in association with COVID-19 have recently been seen.[32] An over-emphasis on the fact that NCS and EMG are within normal limits in the first 1-2 weeks in diseases of the muscle and nerves cannot be made. Unnecessary procedures should be avoided as the machines may serve as fomites.

Laboratory evaluation:
Laboratory findings in patients with COVID -19 include high white blood cell counts, lower lymphocyte count, and increased C-reactive protein. Severe infection has corresponding higher D-dimer levels, increased lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase levels, with elevated blood urea nitrogen, creatinine levels and creatine kinase (CPK) levels.

Management:
Patient with neurological manifestations and COVID 19 may require hospitalization with intensive care monitoring. Minimal exposure of healthcare and still providing the best possible care to patients should be the aim.

Long term neurological complications of SARS and other corona viruses:
Delayed neurologic sequelae after 2 weeks of respiratory issues have been described following both SARS-CoV-1 and MERS-CoV infection, such as peripheral neuropathy, myopathy, Bickerstaff brainstem encephalitis, and GBS.[33,34]
Although there is limited data for COVID-19-related psychiatric symptoms currently, survivors of SARS-CoV were clinically diagnosed with post-traumatic stress disorder (54.5%), depression (39%), pain disorder (36.4%), panic disorder (32.5%), and obsessive compulsive disorder (15.6%) at 31 to 50 months post-infection, a dramatic increase from their pre-infection prevalence of any psychiatric diagnoses of 3%.[35] Parkinsonism is a late feature of encephalitis lethargica, first described following the influenza pandemic of 1918.[36] While features of Parkinsonism have not been described in association with CoV outbreaks, anti-CoV antibodies have been identified in CSF of individuals with Parkinson's disease. It is plausible that this could contribute to a delayed neurodegenerative process but this remains to be seen in COVID-19.

Prognosis:
Neurological manifestations may have a variable prognosis. Patients with milder disease or isolated symptoms such as anosmia, ageusia, isolated headaches or myalgias suggest a relatively better outcome. However, those with more severe systemic disease and extensive neurological involvement like strokes, encephalitis or Guillain Barre syndrome may have a graver outcome.

Future directions for research:
Understanding the full spectrum of the neurotropic effects of COVID 19 is still in its maiden stages. Neurological manifestations until now have depicted the entire neuroaxis is prone to disease. Pharmaceutical research needs to change directions to expedite the development of a possible vaccine and also accelerate in the quest for newer antiviral agents. More extensive neurological workup or autopsies and isolation of SARS CoV 2 from neural tissue may help in aiding us to understand the mechanism of COVID 19 better. Management protocols may need to be revised as we learn more about neurological complications every day.

CONCLUSION:

A multi-disciplinary approach is required to control this massive challenge faced by humanity. Health care providers should keep a close watch for isolated neurological symptoms at presentation when evaluating patients for COVID 19 to assure both appropriate management and control of disease. A directed neurological examination limiting exposure of medical personnel to potentially infected patients is mandatory. Appropriate constrained investigations should be considered only if there is a likelihood of changing management. Research for new anti-viral drugs and the development of a possible vaccine is cardinal for the management. Tele neurology consultations whenever possible is the need of the hour. Outcomes of COVID 19 patients with severe illness and neurological complications remains grave

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Conflict of interest: Author declares no conflict of interest.
Funding disclosure: Nil

Author's contribution:
Dureshahwar Kanwar; concept, data collection, data analysis, manuscript writing, manuscript review
Imran Ahmed; data collection, data analysis, manuscript writing, manuscript review
Mohammad Wasay; concept, data collection, data analysis, manuscript review