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Neurological manifestations of Covid-19: A Comprehensive Review

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ABSTRACT

The COVID-19 pandemic causing virus, SARS-CoV-2 emerged in the year 2019 from China. Since then, it has inflicted millions of people globally. Common presentations include cough, fever, body ache, fatigue, and shortness of breath, whereas few people might not develop any symptom. The main target of this virus is respiratory system; precisely it attacks the ACE-2 receptors of alveolar cells of lungs. ACE-2 receptors are also found in heart, gastrointestinal tract, kidneys, testis, and brain; hence involvement of these organs is also seen with this disease. An emerging discovery of invasion of nervous system by this virus has impelled researchers to investigate and understand the neurological mechanisms and features of COVID-19. The virus can affect Central as well as Peripheral Nervous System. Peripheral nervous system implications are not critical and include hypersomnia, ageusia, Guillain barre syndrome, paresthesia, skeletal muscle injury and cranial nerve involvement, whereas in central nervous system, dizziness, headache, acute cerebrovascular disease, altered level of consciousness, transverse myelitis, acute hemorrhagic necrotizing encephalopathy, encephalopathy, encephalitis, epilepsy and ataxia can develop. Neurological manifestations are particularly seen with severely ill COVID patients.

In this article, we present a comprehensive review of prevalence of various CNS and PNS symptoms in COVID-19, risk factors, investigations, management, and prognosis related to these. This will aid the physicians and neurologists in better understanding the course of this illness and the current statistics of neurological presentations, crucial for handling the disease.

Keywords: *Neurological complications, SARS-Cov-2, Neurological signs, Neurological symptoms, Covid-19, Novel Coronavirus.*

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus termed as “severe acute respiratory syndrome”. It’s outbreak emerged in the year 2019 from the Wuhan city, China,[1,2] as unusual cases of pneumonia with an unknown cause.[3] It was proclaimed as a pandemic disease on March 11th, 2020 by World Health Organization (WHO).[4] To this date (29th April 2021) more than 149,216,984 people have been infected worldwide and more than 3,144,028 people have died due to COVID-19.[5] To overcome this outbreak a great amount of research is being conducted regarding it's identification and medical therapy. Studies report a broad spectrum of presentations which include nonproductive cough, fever, myalgia, fatigue, dyspnea, diarrhea, and nausea/vomiting, whereas few patients remain symptomless.[6] Even though COVID-19 predominantly involves the respiratory and cardiovascular system, 35% of the patients are prone to develop neurological symptoms including headache, dizziness, hypogeusia, and neuralgia.[7,8] In some patients, neurological manifestations are the part of the initial presentation,[9] but mostly these are prevalent in patients with severe disease.[10]

In this study we present a comprehensive review of the neurological manifestations of CCOVID-19. Consequently, neurological presentations were bifurcated into Central Nervous System and Peripheral Nervous System symptoms.

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Objective of our study is to upgrade the health care professionals about the neurological manifestations of this novel Corona virus infection.

PATHOPHYSIOLOGY AND CLINICAL ASPECTS OF COVID 19:

The central receptor for the introduction of this infectious agent into cells is Angiotensin Converting Enzyme (ACE-2). After binding of Spike (S) protein of SARS-CoV-2 to ACE-2 receptor, a conformational change in S protein occurs, which leads to fusion of viral envelope with the cell membrane. Genome RNA is released into the cell which then undergoes translation leading to production of protein peptides pp1a and 1ab. These polypeptides are further degraded into smaller proteins by viral enzymes. Additional sub genomic mRNAs are translated into pertinent viral proteins. In the endoplasmic reticulum and golgi apparatus assembly of virion takes place, carried by vesicles towards the cell membrane and released out of the cell.[11]

ACE-2 receptors can be found in the heart, lungs, gastrointestinal tract, kidneys, testis, and brain. The primary site of infection is lungs since ACE-2 receptors are expressed mainly in type 2 alveolar cells of lung. The broad surface of alveolar cells might describe why this organ is vulnerable to damage by SARS-CoV-2 invasion.[12]

A study conducted by Wei- jie Guan et al. on 1099 laboratory confirmed COVID-19 cases, delineated the following clinical manifestations of COVID-19: - Fever (88.7%), cough (67.8%), sore throat (13.9%), sputum (33.7%), fatigue (38.1%), shortness of breath (13.7%), vomiting (5%), diarrhea (3.8%), myalgia (14.9%), and headache (13.6%). Complications developed during hospital admission include septic shock (1.1%), acute respiratory distress syndrome (3.4%), acute kidney injury (0.5%), disseminated intravascular coagulation (0.1%), rhabdomyolysis (0.2%), and physician diagnosed pneumonia (91.1%).[13]

Plasma levels of interleukin 7 (IL-7), interleukin 10 (IL-10), interleukin 2 (IL-2), Granulocyte-colony stimulating factor (G-CSF), Inducible protein IP10, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1a), and tumor necrosis factor-alpha (TNF-α) were comparatively elevated in critically ill patients than non-ICU patients suggesting an underlying hypercytokinemia associated with disease severity. In patients with severe illness, corticosteroids were proved to be beneficial in reducing symptoms, as they decrease inflammation mediated organ damage.[14]

TRIGGERING MECHANISMS OF NEUROLOGIC DAMAGE IN COVID -19:

MECHANISM OF PNS INJURY IN COVID-19:

Chemosensory disturbances such as anosmia and ageusia constitute the main PNS manifestations of COVID-19. The mechanism behind these chemosensory disturbances is briefly described here and outlined in *figure 1.* The model proposed for anosmia is that this virus mainly infects sustentacular cells in the olfactory epithelium, followed by desquamation. The presence of debris in the nasal cavity is indicative of this desquamation. This desquamation process will remove part of the olfactory sensory neurons population and could be accompanied by loss of dendrites of these neurons, where sensory perception occurs leading to anosmia.[15]

The taste buds are renewed after approximately every 10 days. One mechanism for ageusia could be that after infection of taste bud cells, inflammatory cytokines invade the taste buds and impair their regeneration. Toll-like receptors and interferon receptors are highly expressed in taste buds, thus their activation upon contacting the SARS-CoV-2 virus limits taste bud cells renewal and leads to ageusia. Another hypothesis proposed is that damage to cranial nerve fibers concerned with taste(gustation) after invasion of the CNS by SARS-CoV-2 can trigger ageusia. This hypothesis seems to be dubious as many patients developing ageusia had low-severity symptoms without any evidence of CNS involvement.[15]

MECHANISM OF CNS INJURY IN COVID-19:

Possible mechanisms for the entrance of SARS-COV-2 into cells as depicted in the flowchart *(figure 2)* are as follows: The first route is hematogenous and the second is retrograde dissemination of the virus through neurons.[16] In the hematogenous route, SARS-CoV-2 with its spike protein binds to ACE-2 receptors expressed in the capillary endothelium of the blood brain barrier (BBB), neurons and glial cells of the brain especially brainstem and cardiovascular regulatory areas like nucleus tractus solitarius, paraventricular nucleus and rostral ventrolateral medulla. Next, viral particles bud inside capillary endothelium, causing endothelial damage which favors viral entry in the brain.[17,18] The second route is implicated in hyposmia in which the virus enters the olfactory bulb of the brain along the olfactory nerve.[16]

As stated above, the binding of SARS-CoV-2 with ACE-2 receptors promotes the processes of inflammation, coagulation, and apoptosis in vascular endothelial cells of brain thereby increasing the risk of stroke, transient ischemic attack, sub cortical bleeds, micro thrombi, arterial thrombi, venous thrombi, and ischemic infarcts. This hypercoagulable state is due to the elevation of pro-inflammatory cytokines such as TNFα, IL-1β, IL-6, G-CSF, GM-CSF (Granulocyte-Macrophage Colony Stimulating Factor), and chemokines like MCP-1, IP-10 and MIP-1α. This rapid release of large amounts proinflammatory cytokine cause 'cytokine release syndrome or hypercytokinemia' which presents with high grade fever, headache, hypotension, night sweats and multiorgan dysfunction.[19] This high level of circulating cytokines is also associated with confusion and altered level of consciousness.[20] The cytokine storm also causes an alteration in the normal blood coagulation by increasing D-dimer levels, a fibrin degradation product, thereby exerting a pro-coagulant effect.[21] Recent studies also suggest the outcome of this infection on platelets as thrombocytopenia has been identified in those afflicted from severe COVID-19.[22]

Seizure, another manifestation of COVID-19 is proposed to be due to the direct penetration of brain by this infectious agent and by the production of toxins and inflammatory mediators by the virus once it is inside the brain parenchyma.[23] The above-mentioned factors along with some other indirect factors such as hypoxia, dehydration, systemic inflammation and metabolic imbalances are linked to headache recognized in patients affected from COVID-19.[24] The hyperinflammatory state mentioned above is also the likely cause of para-infectious ataxia. Whereas post-infectious ataxia is most likely due to the formation of autoantibodies directed against Purkinje cells, striatal neurons, and hippocampal neurons.[25]

Table 1: shows prevalence rates of these PNS symptoms in different studies throughout the world.

SIGN AND SYMPTOM	STUDY	COUNTRY	SAMPLE SIZE	PATIENTS WITH SIGN AND SYMPTOMS	FREQUENCY
Hyposmia/Anosmia	Klopfenstein T et al.[29]	France	114	54	47%
	Lechian JR at al.[30]	Europe	417	357	85.6%
	Kim GU et al.[31]	South Korea	172	69	39.5%
	Kacem I et al.[32]	Tunisia	646	245	37.9%
Hypogeusia/ Ageusia	Lechian JR et al.[30]	Europe	385	342	88.8%
	Kacem I et al.[32]	Tunisia	646	238	36.8%
	Patel A et al.[33]	London	141	89	63.1%
Guillain Barre Syndrome	Romero-Sanchez CM et al.[34]	Spain	841	1	0.12%
Myalgia	Kacem I et al.[32]	Tunisia	646	241	37.3%
	Patel A et al.[33]	London	141	93	66%
	Gomez-Belda AB et al.[36]	Spain	340	113	33.2%
Paresthesia	C. Ligouri et al.[27]	Italy	103	6	5.8%
	Samar I et al.[37]	Pakistan	350	11	3.1%
Skeletal Muscle injury	Ling Mao et al.[10]	China	214	23	10.7%

Table 2: Table 2 summarizes the CNS manifestations and their incidence in patients with COVID-19

SIGN AND SYMPTOM	STUDY	COUNTRY	SAMPLE SIZE	PATIENTS WITH SIGN AND SYMPTOMS	FREQUENCY
Headache	Mao et al.[10]	China	214	28	13.1%
	Flores-Silva et al.[51]	Mexico	1072	447	41.7%
	Uygun Ö et al.[52]	Turkey	3458	87	33.2% (in 262 Covid-19 positive patients)
Dizziness	Mao et al.[10]	China	214	36	16.8%
	Saniasiaya J et al.[55]	Review article (China, Turkey, USA, Canada, Italy)	1074	141	13.12%
Altered level of consciousness	Mao et al.[10]	China	214	16	7.5%
Cerebrovascular disease	Hernández-Fernández F et al.[60]	Spain	1683	23	1.4%
	Guan WJ et al.[13]	China	1099	11 (Non severe), 4 severe	1.2% (Non severe), 2.3%
	Zhang JJ et al.[61]	China	140	3	2.1%
	Aggarwal G et al.[62]	China	2031	55	2.7%
Seizure	Mao et al.[10]	China	214	1	0.5%
	Lu L et al.[65]	China	304	2	0.65%
Ataxia	Mao et al.[10]	China	214	1	0.5%
Encephalopathy	Meppiel E et al.[67]	France	222	85	38.3%
	Scullen T et al.[68]	USA	76	20	74%
Encephalitis	Meppiel E et al.[67]	France	222	21	9.5%
	Varatharaj A et al.[69]	UK	153	7	44% (out of 16 patients with encephalopathy)

Figure 1: Proposed mechanism of Peripheral Nervous System invasion by SARS-Cov-2.

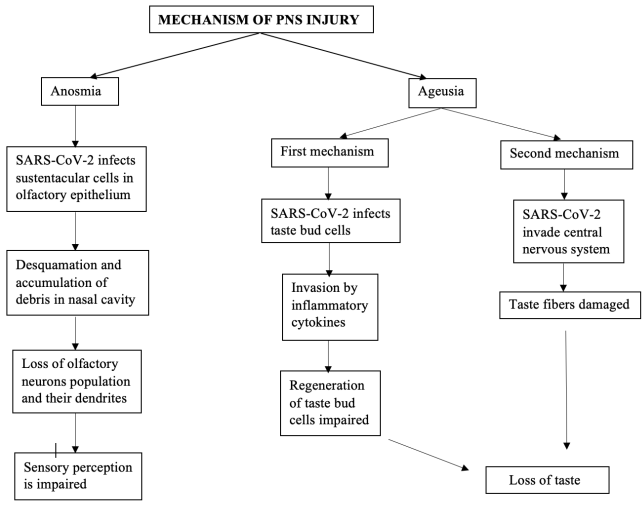
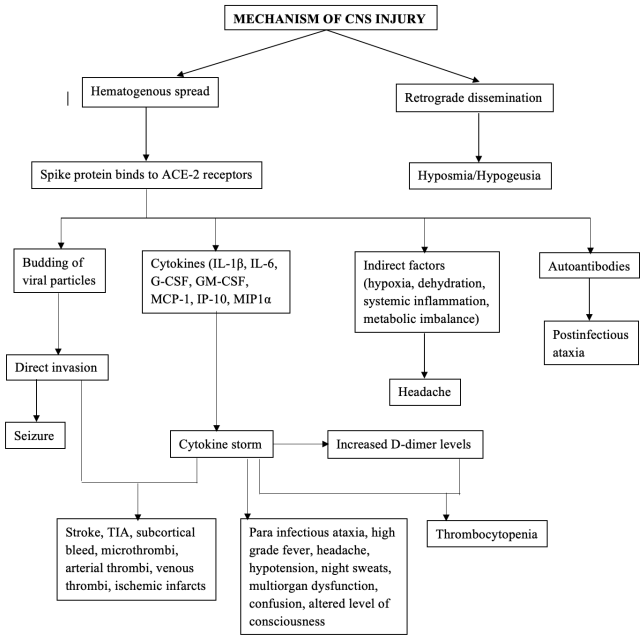


Figure 2: Possible mechanisms of injury in Central Nervous System by SARS-Cov-2.



DISCUSSION

A study done in the early time period of the disease i.e., initial months of 2020, on 214 hospitalized patients in Wuhan province of China from where the virus first emerged, showed few and less severe PNS symptoms, which were less prevalent than the CNS symptoms.[10] These PNS features include hyposmia/anosmia, ageusia, nerve pain, and vision impairment.[10] Later, in a case study, Guillain Barre syndrome was reported in a patient tested positive for COVID-19.[26] Myalgia and paresthesias have also been seen in COVID-19 patients.[27] Myositis/rhabdomyolysis are the other neuromuscular complaints found in this disease.[28] These symptoms as described in different studies are discussed here and summarized in Table 1 below.

Hyposmia or anosmia is a very common presentation. During an observational study by Klopfenstein T et al. in France in March 2020, 47% COVID-19 affected patients with it's definitive diagnosis showed the symptom of anosmia. Participants of this study included both hospitalized and

ambulatory patients but had fewer comorbidities and mainly were middle aged adults. 98% recovery rates from anosmia were observed at the end of study.[29] A higher prevalence of anosmia/hyposmia; 85.6%, was seen in another European study on 417 patients having similar co-morbidity profile and age bracket. Recovery from this ENT symptom was evident.[30] Kim GU et al. delineated the occurrence of hyposmia in an Asian group of population where its prevalence was seen as 39.5%, it was associated with other symptoms in 90% of the patients. Interestingly, hyposmia was even more common than fever.[31] 646 patients with a confirmed diagnosis of COVID-19 were included in a retrospective observational study for the evaluation of neurological implications in Tunisia, North Africa, out of which 37.9% patients reported smell dysfunction. Smell impairment was not associated with nasal obstruction.[32] These studies showed anosmia as a highly prevalent symptom of COVID-19, usually appearing as a second or third symptom during the illness but with a good outcome and associated with a mild to moderate disease course.[30, 31, 32]

Ageusia/dysgeusia in COVID-19 is strongly associated with smell impairment. Klopfenstein T et al. survey described a significant relation between the two symptoms with 85% of patients with anosmia developing dysgeusia too.[29] Similarly, strong association was appreciated between smell and taste dysfunction (p=<0.001) in the multicenter European study. The prevalence rate of dysgeusia was 88.8%.[30] The study of Kacem I et al. in Tunisia also showed simultaneous occurrence of olfactory and gustatory dysfunction in 31.4% patients.[32] While studying the 141 confirmed cases of COVID-19 in UK for the prevalence of anosmia and ageusia, 63.1% reported ageusia. The study concluded that anosmia and ageusia are powerful predictors of COVID-19.[33] Therefore, the presence of these should raise high suspicion of this infection, especially when not associated with nasal obstruction.[32, 33]

Guillain barre syndrome has also come into consideration to be accompanied with this infection. The first case report on GBS is of a 65-year-old male patient, with type 2 diabetes mellitus, who presented with a 5 days history of progressive weakness in distal lower limbs. Weaknesses ascended to proximal limbs and involved all four limbs. Bilateral facial paresis was noted. Deep tendon reflexes were absent. He had no spine sensory level and reduced vibration and fine touch senses below ankle joint. Fever, urinary and fecal incontinence were absent. Blood pressure, respiratory rate, heart rate, oxygen saturation and labs were normal. Erythrocyte sedimentation rate (ESR) was raised and C-reactive protein 2+. GBS diagnosis was made on nerve conduction studies and electromyography. Two weeks prior to this presentation, he had cough, fever and dyspnea and was confirmed with SARS CoV-2 infection by Reverse Transcriptase PCR and chest CT.[27] 841 Spanish confirmed COVID-19 hospitalized patients were a part of an observational study that aimed to evaluate neurological manifestations in such patients. The prevalence of GBS came out to be 0.12%, one of the three least prevalent symptoms among the neurological manifestations in this survey, other two being optic neuritis (0.12%) and encephalitis. However, this study was carried out in the beginning of the pandemic.[34] Rahimi K et al. published a review of total 31 known cases of GBS linked to COVID-19 throughout the world up till August 2020. Among these, 29 cases developed GBS following a SARS CoV-2 infection reflecting the typical post-infectious pattern, whereas 2 cases had GBS and COVID-19 at the same time reflecting the para-infectious pattern. This parainfectious onset of GBS has been seen with Zika virus previously. The most common subtype of GBS seen with COVID-19 was acute inflammatory demyelinating polyneuropathy or AIDP. There was only 1 child patient while majority were older adults supporting the idea that GBS is more common in older and male population.[35] Hence, these data suggest that Guillain barre syndrome can be related to COVID-19, but a rare presentation.

Myalgia is a nonspecific but another very common symptom of COVID-19. The African survey by Kacem et al. demonstrated the incidence of muscle ache as 37.3%, being one of the four main neurological complaints in this study. It was observed early during the infection and was most commonly generalized in nature. However, limb and trunk myalgia were frequent too.[32] The frequency of muscle pain was 66% in London survey by Patel A et al. with it being more frequent in community diagnosed than hospitalized patients.[33] Gomez Belda AB et al. compared the neurological symptoms in elderly and young patients. The results showed that myalgia was more common in the non-elderly group i.e., 41%. The frequency of myalgia in elderly was 23.7% and prevalence of myalgia in total sample size was found to be 33.2%.[36]

Ligouri C et al. while evaluating subjective neurological symptoms in COVID-19 patients found that paresthesia occurred in 5.8% of their participants, all of whom were females. Moreover, it appeared along with at least 2 other neurological complaints and never alone.[27] A cross sectional study carried out in Pakistan to assess the prevalence of neurological characteristics indicated the presence of paresthesia in Corona virus infected population. It was the 3rd most common neurological complaint after headache and vertigo, present in 3.1%.[37] A case of peripheral neuropathy associated with COVID-19 was reported in a 40-year-old woman two weeks after her diagnosis of COVID-19. She complained of sudden onset, severe, intermittent lower back and hip pain with numbness and weakness. On examination she had symmetrical non-ascending weakness in both lower limbs, but deep tendon reflexes were intact. Power was 4/5 and sensory ataxia was noted. Her labs were normal except for slightly raised serum lactate dehydrogenase, low vitamin B6 and mild reduction in serum copper. Authors concluded that this case was different from GBS and vitamin B6 deficiency. She was treated with intravenous steroids, intravenous immunoglobulin, gabapentin, duloxetine, tramadol, rehabilitation, and copper replacement.[38]

Paliwal VK et al. published a review on neuromuscular presentations in SARS CoV-2 infected patients. Besides describing myalgia, GBS, myasthenia gravis, olfactory, gustatory, and cranial manifestations, they discussed rhabdomyolysis/myositis related to COVID-19 in 9 male patients. These patients presented with different clinical characteristics including myalgia and limb/generalized weakness. All of them had raised creatinine phosphokinase (CPK) levels, serum ferritin and LDH. Three patients did not have respiratory involvement.[28] Skeletal muscle injury was reported to be associated with severe infection with increased liver and kidney damage in Wuhan study on hospitalized patients. The incidence of muscle injury in the total sample size was 10.7%.[10]

In cranial nerves, there are reports of involvement of optic, oculomotor, facial, and cochlear nerves.[39, 40] There had been a case report of hearing impairment, ageusia and anosmia along with dyspnea on exertion for 3 days in a 61-year-old lady with a positive contact history of SARS-CoV-2. She was admitted for supportive treatment and 3 days later diagnosis of COVID-19 was confirmed with a positive swab test.[41] Another case with similar triad of hearing, smell, and taste loss with a positive contact history but in a younger patient with longer duration of history was seen. The 18-year-old female reported 7 weeks of bilateral sudden sensorineural hearing loss (SSNHL) with nausea, vomiting, vertigo, ageusia and anosmia. Other risk factors for hearing loss were absent. Serum COVID-19 IgG were detected 10 weeks after the onset of her symptoms.[42] However, while commenting on Kilic et al. article about relation of SSNHL with COVID-19 where only 1 out of 5 patients with hearing complaint was COVID positive; Luca PD et al. said that there was not enough evidence to support the notion that hearing loss could occur with this disease. The authors argued that the present-day published writings available does not provide a solid link between COVID-19 and hearing impairment and thus it is not an established finding yet.[43]

Risk factors of PNS symptoms in COVID-19:

Neurological presentations are more prevalent in hospitalized patients and severe infection.[10, 32, 34] As noted in studies, female and younger patients tend to be affected more with impaired smell sensation.[30, 31, 32]

Investigations of PNS symptoms in COVID-19:

Standard laboratory investigations are carried out in neurological patients of COVID-19 including complete blood count (CBC), CRP, D-dimer, creatinine kinase, lactate dehydrogenase, aminotransferase, alanine, aspartate, BUN, and creatinine. In Wuhan study of hospitalized patients there were no noteworthy difference in the labs of positive PNS symptoms patients and negative PNS symptoms patients.[10] Higher creatinine kinase levels are seen in SARS-CoV-2 positive patients with muscular symptoms compared to SARS-CoV-2 negative patients.[44]

Management of PNS symptoms in COVID-19:

For GBS, IVIG treatment is gold standard and has shown good results in GBS linked to COVID-19 [26,35], thus this usual treatment is followed for these patients. There are no standard treatments for most PNS symptoms occurring in COVID-19 like anosmia and ageusia, these may resolve on their own. In case of muscle involvement nutritional support is advised.[45]

Prognosis of PNS symptoms in COVID-19:

As stated earlier, anosmia has good prognosis and recovery rates are high.[29, 30] However, a retrospective cohort study conducted to evaluate new onset headaches during COVID-19 demonstrated that anosmia and ageusia may persist. In this study, patients were followed 1 month after their symptoms had disappeared via teleconsultation. Besides the finding of new onset headaches, the study reported the persistence of anosmia and ageusia in 14.4% and 11.5%, respectively.[46]

Long-COVID is a term used to describe COVID-19 symptoms extending beyond 6 weeks of duration.[47] Persistence of muscle weakness was observed in 63% of the long haulers in Huang C et al. study done in China, and this was the most common complaint. These patients were interviewed after 6 months of their discharge from hospital and the incidence of fatigue was higher in severely ill patients.[48]

Concerning the prognosis of GBS we see that in review of GBS case reports by Rahimi K et al. 5 out of 31 cases were shifted to ICU[35] and a detailed review covering 73 GBS cases from all the continents except Australia by Abu-Rumeilah S et al. showed 72.1% improvement rates; prognosis data was available for 68 instead of 73 cases. Management data was available for 70 cases in which 21.4% required ventilation support due to increasing GBS severity.[49] Hence GBS with COVID-19 also has a good prognosis.

Overall, PNS symptoms associated with COVID-19 have a favorable prognosis. Nevertheless, follow up must be performed to assess and manage the long-term neurological consequences.

CNS related signs and symptoms in COVID-19

Prevalence of CNS symptoms in COVID-19 patients:

Dizziness, headache, acute cerebrovascular disease, altered level of consciousness, cerebrovascular disease, transverse myelitis, acute hemorrhagic necrotizing encephalopathy, encephalopathy, encephalitis, epilepsy, and ataxia are the main CNS manifestations of COVID-19.[50] They are summed up in Table 2 below.

In a retrospective, observational study conducted on a total of 214 patients hospitalized in Wuhan, China, 36.4% patients developed nervous manifestations. Out of these 24.8% patients had central nervous symptoms.[10] In another prospective, cross-sectional, observational study on 1072 adult hospitalized patients of 18 years of age or more in Mexico City, 15.2% patients developed a new neurological complication.[51]

According to the study conducted by Flores-Silva et al., headache was the most common neurological manifestation in 41.7% COVID-19 positive patients at the time of admission.[51] Uygun Ö et al. while studying the headache characteristics and its association in COVID-19 patients reported that 33.2% patients out of 7.96% COVID-19 positive patients developed new onset headache, whereas 44.3% patients had previous headache. Out of these COVID-19 positive patients, 26.6%, 47.7%, 23.4%, and 2.3% (3) participants complained of mild, moderate, severe, and very severe headache, respectively. These headaches were bilateral, analgesic resistant, lasted >72 hours, were more common in males and were associated with anosmia, ageusia, and gastrointestinal symptoms.[52] Another study conducted by Sampaio Rocha-Filho PA et al. on 73 patients admitted in a hospital in Brazil reported 64.4% patients experienced headache associated with COVID-19.[53] Most patients complained of experiencing a headache on first day of symptom onset. The headache was associated with cough in 16.4% patients in whom the headache was of migraine and tension type headache phenotype. 15% patients complained of continuous headache while those with non-persistent headaches experienced episode of 120 minutes. The headache in this study was also associated with hyposmia/anosmia and hypogeusia/ageusia in 38.4% and 39.7% patients, respectively.[53]

On the other hand, Mao et al. reported that dizziness was the most common neurologic symptom (16.8%), headache being the second most prevalent (13.1%).[10] The first case that

reported dizziness as the presenting complaint of SARS-CoV-2 infection was in a 53-year-old female from China. She presented with a 3 dayshistory of sudden dizziness along with dry throat. She was tested positive for Novel Corona virus on 5th day of admission.[54] Routine blood test showed an elevated number of neutrophils and a reduction in the number of lymphocytes. Chest CT also showed areas of high density especially in extrapulmonary areas. Urine test, lumbar puncture, Brain MRI, pure tone threshold, electronystagmography, and CT angiography of head and neck were normal.[54] Saniasiaya J et al. studied 141 patients from 14 articles who had dizziness as their presenting complain. These studies, however, did not investigate this symptom thoroughly and its investigation and treatment, and outcome were discussed in 2 and 1 studies, respectively.[55] The investigations in the first study were electronystagmography, pure tone threshold, brain MRI and the treatment given was betahistine, danshenchuandomazine. The investigations in the second study were bedside neurological examination, brain CT and the treatment given was meclizine, benzodiazepine, steroids, vestibular rehabilitation which resolved the symptom.[56]

Mao et al. also reported 7.5% patients who complained of impaired consciousness during the disease. Of these affected individuals, 14.8 had severe disease while 2.4% had non-severe disease.[10] Kotfis K et al. in another review article proposed that the incidence of delirium was high in severely ill elderly patients admitted in intensive care unit (ICU) and that it was pertained to several factors. These factors included social and epidemiological factors like isolation, quarantine, and increased burden of work among health care professionals, type of medications and treatment given to the patient, and psychological factors like fear, anxiety, and disorientation.[57] Guan WJ et al. while studying a sample population of 1590 patients in China found that unconsciousness was associated with comorbidities like COPD, diabetes, hypertension, cardiovascular disease, cerebrovascular disease, and hepatitis B infection.[58]

Stroke or cerebrovascular disease is a rather infrequent but deadly manifestation of SARS-CoV-2 infection. It occurs in 1-3% and 6% of hospitalized patients and patients admitted in ICU, respectively.[59] Hernández-Fernández F et al. in a single center retrospective analysis done on 1683 patients admitted in a hospital reported that 1.4% patients developed cerebrovascular disease. In this subset of patients, the stroke typically developed 5 days after the onset of COVID-19 symptoms. These patients were further subclassified according to the type of cerebrovascular disease they developed. These included cerebral ischemia, intracerebral hemorrhage, and posterior reversible encephalopathy syndrome (PRES)-type leukoencephalopathy in 73.9%, 21.7%, and 4.3% patients, respectively. The mean age of the patients who developed cerebrovascular disease was 66.9 years and the study also showed a high incidence of disease in male smokers with comorbidities like hypertension, type 2 diabetes mellitus, dyslipidemia, ischemic heart disease, atrial fibrillation, and COPD.[60] While studying 1099 cases of COVID-19 positive patients from 522 hospitals from 30 provinces of China, Guan WJ et al. reported that 1.2% out of 84.2% patients with non-severe disease and 2.3% out of 15.7% patients with severe disease developed cerebrovascular disease. The median age of the patients was 47 (35-58) years and the outcomes in this subset of patients were admission in intensive care unit, mechanical ventilation, and death.[13] Zhang JJ et al., studied a total of 140 patients with a median age of 57 (25-87) years. 2.1% patients developed stroke. Of these 3 patients, 1.2% had non-severe disease while the other 3.4% had severe disease. In this subset of patients, the two most prevalent comorbidities were hypertension (30%) and diabetes mellitus (12.1%).[61] In a pooled analysis of published literature done by Aggarwal G et al. which overviewed a sample population of 2031 in 6 different studies, it was established that cerebrovascular disease correlated with a statistically significant increased risk of severe form of COVID-19 (~2.5-fold increase).[62] Oxley TJ et al. published a study which described stroke in individuals below the age of 50 (33, 37, 39, 44, 44 years). 4 of these 5 patients were males and 1 was female. 2 patients did not have any comorbid conditions while the remaining 3 had hyperlipidemia, mild stroke, hypertension, and diabetes. The mean National Institute of Health Stroke Scale (NIHSS) was 17. The investigations included CT, CTA, computed tomography perfusion (CTP), MRI, and the treatment modalities included apixaban, aspirin, intravenous t-PA, clopidogrel, clot retrieval, stent, and hemicraniectomy.[63]

Mao et al. in their case series also reported 0.5% (1) patient with severe disease who developed seizures.[10] One more case of seizure was reported in a 30-year-old female from Iran with no known comorbidities. The woman developed generalized tonic clonic seizures on 5th day of the onset of generalized symptoms of COVID-19 like dry cough, fever, and fatigue. The first episode of seizure occurred 2 days before admission in the hospital and thereby continued to occur at least 5 times a day and approximately 8 hours apart. The chest CT showed focal ground-glass opacities, whereas all the other laboratory investigations were unremarkable. The patient was given intravenous phenytoin and levetiracetam which helped control the seizures.[64] A retrospective multicenter study conducted by Lu L et al. on 304 patients reported seizures in 2 females of ages 32 and 65 years. The latter developed the symptom due to metabolic abnormalities which was resolved by correcting the metabolic disturbance.[65]

Mao et al. also reported 0.5% (1) patient with severe disease to develop ataxia.[10] The first case of ataxia in a COVID-19 positive patient was reported by Diezma-Martín AM et al. The patient was 70 years old with a history of COPD. Ataxia was developed along with tremor on 17th day of symptom onset. Baseline laboratory investigations, CSF analysis, and brain MRI showed no evidence of disease. The symptom was initially thought to be a consequence of treatment with corticosteroids and beta-adrenergic drugs, but it did not resolve when these drugs were withdrawn. Clonazepam caused a slight improvement of symptom.[66]

Meppiel E et al. conducted a retrospective, single-center observational study on 222 hospitalized patients in 46 hospitals in France and reported that 38.3% patients had encephalopathy, 28.4% had stroke, 9.5% had encephalitis.[67] Scullen T et al. conducted a single-center cross-sectional analysis of 76 patients in Louisiana. The mean age of the patients was 59.8 years and the predominant comorbid conditions that these patients had were hypertension, type 2 diabetes mellitus, obesity, and chronic kidney disease. 74% patients were diagnosed with COVID-19 associated encephalopathy. This diagnosis was established based on EEG, brain CT and/or brain MRI.[68] Varatharaj A et al. while conducting a survey of 153 cases in UK reported 16 patients with encephalopathy. Out of these 16 patients, 44% (7)

patients showed signs of CNS inflammation and met the criteria for clinical diagnosis of encephalitis.[69] A few postinfectious syndromes are also associated with COVID-19 patients. These include, acute demyelinating encephalomyelitis (ADEM), acute hemorrhagic encephalitis (AHE), acute hemorrhagic necrotizing encephalopathy, and transverse myelitis. The first case of postinfectious acute transverse myelitis was published by Durrani et al. in a case report. The patient was a 24-year-old male with no known comorbidities. He came to hospital with the complaint of general COVID-19 symptoms and his nasopharyngeal swabs were tested positive for SARS-CoV-2 on RT-PCR. He was admitted in hospital for 3 days and was given symptomatic treatment. He then presented 9 days later with bilateral lower limb weakness with overflow urinary incontinence. He had bilateral knee and ankle reflexes, and bilateral lower extremity flaccid paraplegia. Other neurological findings were unremarkable. MRI spine showed hyperintense signal abnormality seventh to twelfth thoracic vertebra, a finding associated with acute transverse myelitis. Lumbar puncture also showed lymphocytic pleocytosis. The patient was then given IV methylprednisolone which improved the bilateral lower limb strength.[70] Poyiadji et al. reported the first case of acute hemorrhagic necrotizing encephalopathy in a female airline worker in her late fifties. The patient presented with cough, fever, and altered mentation foe 3 days. Nasopharyngeal swab was done, and she was tested positive for COVID-19. Non-contrast CT of head showed symmetric hypoattenuation of bilateral medial thalami. Whereas MRI showed hemorrhagic rim enhancing lesion in bilateral thalami, medial temporal lobes, and subinsular region. CSF cultures were negative for any other causative agent and CT angiogram and venogram were normal as well. The patient was given intravenous immunoglobulin. This case of ANE was thought to be caused by cytokine storm.[71] A 53-year-old man was hospitalized after developing general symptoms of COVID-19. His condition deteriorated rapidly, and he was admitted in the critical care unit the next day. He was diagnosed with ADEM 59 days later for which he was given intravenous methylprednisolone followed by prednisolone. His case was later followed up neurorehabilitation unit. The investigations included MRI of brain and orbits with gadolinium (multiple bilateral hyperintense lesions in subcortical and deep white matter of frontoparietal lobes), fluid-attenuation recovery sequence (FLAIR) (sulcal hyperintensities in parieto-occipital lobes, susceptibility-weighted imaging sequence (parenchymal microhemorrhages in frontal, parietal, and occipital lobes), elevated D-dimer, oligoclonal bands in both CSF and serum, diffuse slowing with transient sharp theta waves in EEG, reduced visual acuity, and marked colour deficit in Ishihara test.[72] Chaumont et al. reported a COVID-19 patient with meningoencephalitis. His symptoms were fever, cough, altered level of consciousness, confusion, severe headache, neck stiffness, anosmia, ageusia, cervical pain, inability to walk, dyspnea, and diarrhea. Laboratory investigations showed increased C-reactive protein, creatinine kinase, lactate dehydrogenase, and liver enzymes. CSF was purely lymphocytic, and EEG showed bilateral slowed activity. Chest CT was highly suggestive of COVID-19. SARS-CoV-2 was not detected in nasopharyngeal swab or CSF but was present in bronchopulmonary lavage. The treatment modalities included nasal oxygen therapy, acyclovir infusions, hydroxychloroquine sulfate, and azithromycin. His symptoms improved with time although he had mild symptoms when he was discharged.[73]

Risk factors of CNS symptoms in COVID-19 patients:

Old age and critical illness are two important risk factors for delirium in COVID-19 positive patients.[57] Other modifiable risk factors include excessive use of benzodiazepines for sedation and a decrease in the number of visits from family members of admitted patients.[74] A cross-sectional study demonstrates female gender, history of headache disorders, fever, dehydration, malignancy, decreased platelets and hemoglobin levels and an increase in neutrophil to lymphocyte ratio (NLR) and CRP as important risk factors for headache associated with COVID-19.[75] Old age, race other than Caucasian, need for mechanical ventilation and use of anticoagulants can lead to intracerebral hemorrhages in COVID-19 patients.[76] Other important risk factors for stroke were severely ill male smokers who were admitted in ICU and had comorbid conditions like hypertension, type 2 diabetes mellitus, dyslipidemia, ischemic heart disease, atrial fibrillation, and COPD.[59, 60] Lu L et al. in his retrospective multicenter study proposed that 27% cases were at high risk of developing seizures with hypoxia being the most important risk factor. Shock, sepsis, imipenem use, acute cerebrovascular disease, traumatic brain injury, multiorgan dysfunction syndrome, and hypoglycemia are important risk factors as well.[65]

Investigations for CNS symptoms in COVID -19:

Laboratory investigations included routine blood test, urine test, lumbar puncture, brain MRI, brain CT, pure tone threshold, electronystagmography, EEG, CT angiography of head and neck and CTP.[54, 68] Another study showed that patients with elevated D-dimer levels present with neurological symptoms in COVID-19.[77]

Management of CNS symptoms in COVID-19:

Dizziness in COVID-19 was treated with meclizine, benzodiazepine, steroids, vestibular rehabilitation.[56] For stroke, treatment modalities included apixaban, aspirin, intravenous t-PA, clopidogrel, clot retrieval, stent, and hemicraniectomy.[63, 78] For seizures, antiepileptic drugs like phenytoin, valproic acid, levetiracetam, zonisamide were prescribed to the patients.[79] Ataxia was relieved by clonazepam.[66]

Prognosis of CNS symptoms in COVID-19:

A retrospective study conducted by Eskandar EN et al. on 4711 COVID-19 positive patients showed that 12% patients had neurological manifestations. Out of these patients 44% patients had an altered level of consciousness, 4% patients had seizure, and 4% patients had other brain lesions. The remaining patients in this subgroup had normal level of consciousness. The patients who have had stroke and altered mentation had the highest mortality rate when compared with other COVID-19 positive patients i.e., 49% vs 24% and 40% vs 33%, respectively.[80]

CONCLUSION

In the light of the available literature, it is evident that Novel Corona virus can invade nervous system both directly and indirectly and can produce a wide array of signs and symptoms in both CNS and PNS. It is therefore important that healthcare workers from around the globe must have ample knowledge of these neurological manifestations. As stated above from multiple studies, these neurological symptoms

can even constitute the first presenting symptom in COVID-19 positive patients, therefore, the possibility of any patient presenting with neurological manifestations to have concomitant SARS-CoV-2 infection should always be kept in mind. The need to further evaluate and assess more possible neurologic signs and symptoms associated with COVID-19 is therefore crucial for the better treatment and reduction in morbidity and mortality in all such patients. We therefore urge that more studies should be conducted on the above topic for better understanding and management of the disease.

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