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Review Article

Brain Disorders at Admission, During and After SARS-CoV-2 Infection

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Abstract

The potential involvement of SARS-CoV-2 in Central Nervous System (CNS) has attracted considerable attention because of the neurological and psychiatric manifestations presented throughout the disease process. There have been many reports of extra respiratory manifestations, such as neurological and psychiatric symptoms at the admission of the patients in the Hospitals, during and after SARS-CoV-2 infection. The seriousness of the virus in various parts of the body will determine what comes after the initial phase. The main brain symptoms and brain disorders that are described in many studies at admission during and after infection are: impaired memory (34,1%), dizziness (7,9 - 16,8%), headache (3,7 - 90,5%), stroke (2,8 - 8,1%) (cerebral infarction (1,6%), venous thrombosis, intracerebral, or subarachnoid hemorrhage), meningitis/encephalitis, and acute necrotizing hemorrhagic encephalopathy, impaired consciousness (7,5 - 7,8%), seizures (1-1,5%), loss of sense of smell (hyposmia (14,5% - 35,6%---34%)) or taste (hypogeusia (12,5%---34%), depressive symptoms (35%), depression (47,1% - 14,9), suicidality (2%), delirium/confusion (27,0%-27,9%), insomnia (41,9%---12,1%---100%), anxiety (35,7%---14,8%), somatization (45,9%), psychosis (3,9---4,4), and post-traumatic stress disorder (96,2% - 32,2%). Unfortunately, all these percentages are changing every day and perhaps we'll have the reliable numbers at the end of the COVID-19 pandemic, which we wish to be very soon.

Keywords: Covid 19; Brain Disorders; Neurological and Psychiatric

Introduction

The coronavirus disease 2019 (COVID-19) is an infectious disease caused by SARS-CoV-2 that primarily affects the respiratory system, as acute respiratory distress syndrome (ARDS) and interstitial pneumonia. The predominant symptom of human coronaviruses is respiratory involvement, with acute respiratory failure being the leading cause of death. There are many target organs of the SARS-CoV-2 infection, including the lungs, heart, kidneys, gut, brain and blood vessels. As such, a multidisciplinary approach becomes crucial for the evaluation and the follow-up of patients with COVID-19. According to recent reports, the involvement of CNS usually occurs during the infection, but neurological manifestations may be the presenting features of SARS-CoV-2 There have been reports of neurological and psychiatric symptoms during and after SARS-CoV-2 infection [1], In Mao., *et al*. from 214 patients with COVID-19 who were studied, 78 (36.4%) had neurological manifestations, which were grouped into four main categories: acute cerebrovascular disease, impaired consciousness, peripheral nervous system involvement and muscular manifestations [2]. In a report by Li., *et al*. out of 221 patients with COVID-19, only 13 de-

veloped acute cerebrovascular disease with cerebral infarction, venous thrombosis and intracerebral hemorrhage.

Unfortunately, there may be some serious signs of potentially fatal brain disorders in recovering patients that doctors have missed. Neurologists have reported that they have never seen these effects in the brain caused by any other viruses. Fortunately, until now only a small number of patients appeared to experience serious neuropsychiatric complications and that more work is needed to understand their prevalence.

Coronaviruses may induce cognitive, emotional, neurovegetative, and behavioral dysregulation through biological mechanisms, including direct neuro-invasion and triggering of immune activation. Increasing evidence has linked immune activation with depression and suicidal behavior, and according to several large meta-analyses, anti-inflammatory approaches have demonstrated efficacy in treating depression [3].

Even after recovering from COVID-19, patients may still experience problems with breathing, fatigue, weakness, numbness, memory problems, and other severe psychiatric symptoms that require anti-psychotic medication. It is useful for all physicians, GPs and healthcare workers with patients with these symptoms to discuss the case with neurologists and psychiatrists. With more research, we can understand how exactly this infection affects the brain.

Neurologic symptoms from the CNS

Severe COVID-19 may affect the CNS and have various acute or delayed neurological complications. During the COVID-19 pandemic, it is crucial to consider COVID-19 infection when seeing patients with neurological symptoms. Mao., *et al*. investigated the penetration potential of COVID 19 into the CNS in 214 patients. They reported that about 36% of the patients had neurological findings that ranged from nonspecific manifestations, e.g., dizziness, headache, and seizure, to specific manifestations, e.g., loss of sense of smell (hyposmia) or taste (hypogeusia), and acute cerebrovascular disease (acute ischemic stroke, cerebral venous sinus thrombosis, cerebral hemorrhage, subarachnoid hemorrhage), meningitis/encephalitis, and acute necrotizing hemorrhagic encephalopathy. Some other authors reported also confusion, agitation, delirium and stupor. Although it is unknown whether these common symptoms are related to COVID-19, it is still important to mention here that dramatic neurologic symptoms, such as depressed level of consciousness, seizure, and stroke, are common in the patients at the late stage of the disease, accounting for increased mortality rate in severely affected patients. Nevertheless, to objectively delve into the direct relation between the neurologic symptoms and COVID-19, medical comorbidities of patients should also be considered [4]. There is a big difference between studies about the incidence of each neurological or psychiatric symptom. The reason for this difference between the various reports remains unclear.

Mechanisms of CNS involvement

The mechanisms of CNS involvement are not clear yet. Perhaps because it is a recently identified disease, COVID-19 has been principally identified by its prominent symptoms such as fever, cough, and dyspnea and not the less common neurological manifestations such as headache, dizziness, and chemo-sensitive impairment SARS-CoV-2 may affect CNS through two direct routes (hematogenous dissemination or neuronal retrograde dissemination) or through indirect routes [5]. Recent reports suggest potential mechanisms leading to SARS-CoV-2 neuro-invasive and neurotropic characteristics. Coronavirus can damage the CNS through several mechanisms including 1. direct infection, 2. hypoxia, 3. ACE-2, 4. immune-mediated, or unpredictable effects of the host immune response and 5. indirect damage of the CNS due to one or more systemic diseases.

The first is direct viral damage to the CNS via blood circulation or nasal epithelium

Coronaviruses appear capable of directly invading the CNS through neural and hematogenous routes. The neural pathways involve the virus going to the CNS from the nasal cavity and rhinopharynx by way of the olfactory and trigeminal nerves and from the lower respiratory tract through the vagus nerves. The hematogenous neuro-invasion occurs via the bloodstream and includes 3 components that rely on which cell is infected by coronaviruses on their path toward the CNS. These include (1) leukocytes (predominantly monocytes) that are a vehicle of transportation to the CNS, (2) endothelial cells related to the blood-brain barrier, or (3) endothelial cells of the blood-cerebrospinal fluid barrier stationed in the ventricles of the brain, specifically in the choroid plexus. The second cause of CNS damage is hypoxia. As we mentioned above the COVID-19 is an infectious disease caused by SARS-CoV-2 that mainly affects the respiratory system, as interstitial pneumonia and acute respiratory distress syndrome (ARDS), which has as a result hypoxia of many organs. Hypoxic encephalopathy has been diagnosed in 20% of 113 deceased patients with the virus [6]. The

third one is that SARS-CoV-2- is comparable to SARS-CoV and both bind to the angiotensin-converting enzyme 2 (ACE2) receptor to penetrate human cells. Angiotensin-converting enzyme 2 (ACE-2) and dipeptidyl peptidase 4 (DPP4) receptors are not commonly expressed in the CNS except in specific circumstances, such as temporal lobe epilepsy and neurodegenerative disorders [7]. ACE2 is found on non-immune cells, such as respiratory and intestinal epithelial cells, endothelial cells, kidney cells (renal tubules) and cerebral neurons and immune cells, such as alveolar monocytes/macrophages. Thus, cells expressing ACE2, such as neurons and glial cells, are like targets and thus susceptible to SARS-CoV-2 infection. The fourth cause of nervous tissue damage comes from the unpredictable consequences of the host immune response after an acute infection. Perhaps delayed autoimmunity, Guillain-Barré syndrome (GBS) is an example, as peripheral demyelination. The fifth mechanism is indirect damage of the CNS due to one or more systemic diseases, particularly in patients who are seriously ill. The last mechanism is hyperactivation of the immune response, which leads to cytokine release [8]. However, the cytokine secretion and bloodstream circulation (viremia) are some of the most likely routes into the nervous system.

Interest has been directed to the use of angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), because these drugs may affect the ability of COVID 19 to infect cells through upregulation of angiotensin-converting enzyme 2 (ACE2), the receptor for SARS-CoV-2- cell entry. Based on this suggested mechanism, opinion leaders strongly suggest that data do not support discontinuation of ACEI/ARBs and have requested outcome studies. Current studies show that prior use of ACEI/ARBs was not significantly associated with COVID-19 diagnosis among patients with hypertension or with mortality or severe disease among patients diagnosed as having COVID-19. These findings support continuing ACEI/ARB medications that are clinically specified in the context of the COVID-19 pandemic.

Stroke

Thrombotic events may be the initial presenting symptom of COVID-19. These thrombotic events include stroke, venous thromboembolism, pulmonary embolism and cardiac complications. Clinicians should be aware of the risk of thrombosis in patients positive for COVID-19, including prophylaxis and treatment beyond discharge.

It was not clear whether COVID-19 was associated with an increased risk of ischemic stroke than would be predicted from a viral respiratory infection. However anecdotal reports and clinical observations have recently suggested a relationship between COVID-19 and stroke, emphasizing the possibility that infected individuals may be more likely to experience cerebrovascular events.

There are many studies in different countries which describe a co-existence of COVID 19 and stroke. However, these studies lacked appropriate control groups. It was useful to assess whether COVID-19 is associated with an increased rate of ischemic stroke than would generally be predicted from a viral respiratory infection. A recent retrospective cohort study from 2 New York City academic hospitals showed that approximately 1.6% (31/1916) of adults with COVID-19 who visited the emergency department or were hospitalized experienced ischemic stroke, a higher rate of stroke compared with a cohort of patients with influenza (0,2%, 3/1486) [9].

However, the existence of cerebrovascular events in patients with arterial hypertension and cardiovascular disease is perhaps related to a direct effect of the infection itself or an inappropriate host response. Though in case reports and small series, the possibility of coincidence cannot be excluded [10].

Mechanisms of stroke

A focus on the thrombo-inflammatory pathways, can be discussed. Some of these possible mechanisms are not new but are, in fact, long-standing hypotheses connecting stroke with preceding infection and are not yet confirmed. Although COVID-19 is mainly a respiratory illness, studies suggest that it may lead as the majority of infections to a hypercoagulable state and thrombotic complications. A 31% occurrence of thrombotic complications in ICU patients with COVID-19 infection has been reported in 184 ICU patients with proven COVID-19 pneumonia, of whom 23 died (13%) [11]. However, there was a significant decrease in amount of admissions for stroke and TIAs during the lockdown due to COVID-19 in Norway. There are worries that public anxiety around COVID-19 dissuades patients from seeking medical help [12]. We believe that the same happened in many other countries all over the world during this period.

Multiple sclerosis

SARS-CoV2 immunopathology and tissue colonization in the gut and the central nervous system, and the systemic inflammatory response during COVID-19 may potentially trigger chronic autoimmune disorders.

Patients with multiple sclerosis (MS) treated with immunomodulating pharmacological agents may have a higher risk of becoming infected with SARS-CoV-2 and associated complications. Proper management of the clinical pharmacological aspects of the MS patient is of paramount importance especially in this period of the COVID-19 pandemic. The data show that the MS patient has a higher risk of infection (about + 40%) than the general population and the most frequent hospitalizations are caused by respiratory and urinary tract infections. This is why the MS patient is fragile, and in this pandemic period, must be closely monitored.

Specifically, multiple sclerosis presents several pathogenic mechanisms that can be hypothetically initiated by SARS-CoV2 infection in susceptible individuals. Some authors present the clinical evidence supporting the investigation of SARS-CoV2 infection as risk factor for this neurological disorder. Thanks to these treatments, it is possible to keep the disease under control for many years, but these remedies can also lead to severe reactions with adverse effects and a higher risk of viral, bacterial, and fungal infections Some suggest the opportunity to perform in the future SARS-CoV2 serology when diagnosing this disorder.

MS may come from past SARS-CoV2 infection caused by several mechanisms: (1) a "challenging" effect of the virus in susceptible subjects previously exposed to priming pathogens; (2) unbalance of peripheral lymphocyte subsets and massive cytokine release producing a pro-inflammatory environment and triggering autoimmune reactions; (3) induction of post-infectious demyelinating events associated with direct CNS invasion and microglial reaction [13].

Many treatments of MS can control the disease for years, yet these therapeutic agents can also lead to serious reactions with grave effects and a higher risk of viral, bacterial, and fungal infections. The safety profile of IFN-β and glatiramer has been assessed in multiple studies; the most frequent severe reactions documented are flu-like symptoms and injection site reaction. At the moment, though, they appear to be the safest drugs to lessen the risk of infection. Fingolimod can lead to adverse reactions, and the most frequent are urinary and lower respiratory tract infections. These reactions are thought to be caused by the reduction of lymphocytes in the blood. The utilization of teriflunomide and dimethylfumarate shows that these drugs lead to a small decrease in white blood cell counts that could make the patient susceptible to serious infectious risks. Severe events of ocrelizumab concerning allergic reactions are because of infusion, itching, rash, hives, hyperglobulinemia, and lymphocytopenia associated with secondary infections. Given recent studies, MS patients being treated with these drugs should be carefully supervised for any increased risk of infection related to the drugs and the disease. Medications such as IFN-β and glatiramer seem to be a safer option; ocrelizumab or cladribine appear to lead to a more increased risk of infection than other drugs [14].

Coronavirus probably enters the CNS through the olfactory bulb, which could cause inflammation and subsequent axonal damage or demyelination (Desforges, M. 2020). The cases published by Paterson, revealed a rise in a life-threatening condition called acute disseminated encephalomyelitis (Adem), as the first wave of infections swept through Britain. At UCL's Institute of Neurology, Adem cases rose from one a month before the pandemic to two or three per week in April and May. One woman, who was 59, died of the complication [15]. In the same study the authors refer that 12 patients had inflammation of the CNS, 10 had delirium or psychosis and 8 had strokes.

Headache

Headache is the most frequently recorded neurological COVID-19 symptom. A systematic review of 554 COVID-19 patients suggests that the rate of occurrence of headache is about 8% [30]. The study of the NYC with a sample of 1000 patients found that the only brain symptom which was recorded was headache with a prevalence of 10,1% [16].

A study examined 10 patients with fracture and Covid-19 and 1 of them reported headache as a symptom [17]. A case-series study of 12 Covid-19 patients in Jilin Province, China found that 3 of the patients studied had headache as a symptom [18]. A study of 21 patients infected with Covid-19 in a tertiary care center in India showed that headache was present in 13.6% of them [19]. A study of 48 confirmed cases of Covid-19 patients in Hengyang, Hunan Province, China found that 10.4% of them had headache as a symptom [20]. In a retrospective, single-centered, observational study of 51 critically-ill patients with Covid-19 pneumonia that were admitted to the ICU in Wuhan, China, 6% of them had headache as one of the main presenting symptoms [21]. A study of 60 patients with Covid-19 found that headache was present in 12.73% of the population studied [22]. A study of 62 patients infected with Covid-19 outside of Wuhan, China showed that headache was present in 34% of the patients [23]. A retrospective multicenter study was comprised of 64 Covid-19 patients who had neurological symptoms

and then had a brain MRI. Headache was present in 16% of those patients [24]. A retrospective study in Egypt including 66 Covid-19 patients, 36 of them had mild to moderate disease and 30 of them severe/ critical infection. Headache was a symptom in 22.2% of the first group and 33.3% of the second group [25]. A study comparing the clinical characteristics between 70 Covid-19 patients and 54 influenza patients in Norde Franche-Compte Hospital found that 26% of the Covid-19 infected patients had frontal headache compared to 9% of the influenza patients [26]. In a retrospective study looking at the radiological findings of 81 patients with confirmed Covid-19 pneumonia in Wuhan, China 6% of the patients had headache as one of the presenting symptoms [27]. A study by Tostman., *et al*. questioned 90 health care workers in the Netherlands positive for Covid-19 infection, 71.1% of them reporting that they had headache as a symptom [28]. In another single-center, retrospective study of 99 patients with Covid-19 pneumonia, it was shown that 8% of the studied population presented with headache [29].

A systematic review and meta-analysis of 29 publications by Koh., *et al*. regarding 533 Covid-19 adult patients found that headache was a symptom in 10% of the population studied [30]. An additional systematic review of 554 COVID-19 patients found that the average frequency of headache was 8% (Rodriguez-Morales AJ, 2020). In a study by Trigo., *et al*. 576 Covid-19 patients were assessed for neurological manifestations and 137 of them (23.7%) said they were experiencing a headache**.** The patients reported having a headache before their ED consultation in 124/137 (90.5%) cases. Headache was the beginning symptom in 27/104 (26.0%) of patients and appeared within a day (24 hours) in 40/104 (38.5%) of patients, within two days in 65/104 (62.5%) of patients, and within three days in 77/104 (74.0%) of patients [58]. A study about the epidemiological and clinical characteristics of 645 Covid-19 patients found that of the 573 patients with abnormal imaging findings, headache was present in 11.3% of the patients [31]. A retrospective study by Jin., *et al*. examined 651 Covid-19 positive patients, out of which 74 had at least one gastrointestinal symptom. Of those patients, 21.62% reported headache as a symptom as well [32]. A case series of 655 Covid-19 positive patients in Henan Province, China found that headache was reported by 12.2% of the population studied [33]. A study by Lian., *et al*. studied the clinical and epidemiological characteristics of COVID-19 patients in Zhejiang Province with and without history of Wuhan exposure. They discovered that headache was significantly lower in the exposure group than that in the control (6.87% vs. 12.15%) [34]. A study of 841 Covid-19 patients in Spain found that 14.1% of them had headache as symptom [35].

A study by Guan., *et al*. of 1099 patients with laboratory - confirmed Covid-19 in China showed that 14% of the patients reported headache as a symptom [36]. A review by Long-Quan Li., *et al* concerning the data of 1994 patients showed that headache and dizziness was found in 12.1% of the studied population [37]. A study of 1420 European patients that evaluated the clinical and epidemiological characteristics of mild-to-moderate Covid-19 infection discovered that headache was a very common symptom reported in 70.3% of the patients [38]. A study examining the clinical features of 1487 COVID-19 patients with outpatient management in the Greater Paris found that headache was reported by 55% of the studied population [39]. A 17-question online survey regarding neurological symptoms of COVID-19 patients was made available on the European Academy of Neurology website and distributed to its members and proper data was collected by 2343 responders. The most frequently reported neurological finding was headache (61.9%) [40]. A meta-analysis of 3062 Covid-19 patients by Zhu., *et al*. reported that headache was present in 15.4% of the patients [41]. A systematic review and meta-analysis by Kumar., *et al*. regarding 6,892 Covid-19 patients found that headache was a symptom in 11.2% of the studied population [42]. A systematic review and meta - analysis, by Pinzon., *et al*. of 33 studies regarding 7,559 Covid-19 patients found that headache was symptom in 10.9% of them [43]. A meta-analysis by Zhu., *et al*. of 55 unique retrospective studies involving 8697 patients with COVID-19 found that 11.3% of the patients had headache as a symptom [44].

A systematic review and meta-analysis by Abdullahi., *et al*. regarding 11,069 Covid-19 patients found that headache was a symptom in 12% of the studied population [45]. A systematic review of neurological symptoms and complications by Chen at al., analyzed 51 studies involving 16,446 patients with Covid-19, headache was reported in 20.1% of the studied population, ranging from 2.0 to 66.1% [46]. A review by Nascimento., *et al*. of 61 studies regarding 59,254 patients with Covid-19 infection concluded that headache was one of the most common disease related symptoms with a prevalence of 12% [47]. A systematic review by Nepal., *et al*. of 37 papers found that an overall average of 19.88% of Covid-19 patients experienced headache [48].

Paterson., *et al* described a woman, aged 47, who was admitted to the hospital because of a headache and numbness in her right

hand, which appeared a week after a cough and fever started. Later, she was drowsy and unresponsive and needed emergency surgery to take out part of her skull to alleviate pressure on her inflammed brain.

Impairment of consciousness: confusion, delirium, somnolence, stupor and coma

Confusion and headache were the fifth (9/99 [9%]) and sixth (8/99 [8%]), respectively, most frequent symptoms of 99 COVID-19 patients upon hospital admission [49]. In specific, impaired consciousness, like confusion, delirium, somnolence, stupor and coma, have been reported more often in patients with severe infection (14,8%) occurring later in the illness. Confusion and delirium is a common symptom in the elderly. A cohort study in a Dutch nursing home did not find significant statistical difference of confusion and delirium among residents (mean age = 84 years, SD = 8,7 years) tested positive and negative for COVID-19, but a positive COVID-19 test increased the likelihood of dying in the next 30 days more than twofold (48% of positive tested residents) (Chen X., *et al*. 2000). A systematic review of neurological symptoms in patient positive for COVID-19 found that the frequency of reported impairment of consciousness in all patients with COVID-19 was 5,1%, analyzed further in mild to moderate infection 3,2% and in severe infections 11,9%. Impairment of consciousness and meningoencephalitis have been reported as the first symptom of infection in immunosuppressed patients with COVID-19 infection recurrence with CSF samples tested positive 21 days after initial infection [50]. Similarly, another case report of a young female patient presenting only with lethargy and meningoencephalitis without respiratory symptoms had poor response to initial treatment for viral meningitis but was tested positive for COVID-19 and treated successful with the addition of hydroxychloroquine [51]. Another interesting case report concerning a male patient positive for COVID-19 presenting with fever, shortness of breath, impairment of consciousness, meningeal irritations signs and high CSF pressure (220 mmH_2O) that was diagnosed with encephalitis due to COVID-19 infection and treated successfully with supportive treatment and mannitol infusion [52]. Plasmapheresis is also considered a possible treatment option for autoimmune meningoencephalitis due to COVID-19 and prolonged ICU admission. Meningoencephalitis and impairment of consciousness is often seen as the neurological manifestation of COVID-19 infection, as concluded by a systematic review [53]. Unfortunately, detection of COVID-19 in CSF samples is in most cases not possible due to characteristics of the illness or due to technological limitations.

Mechanisms of impairment of consciousness

The exact mechanism of COVID-19 causing impairment of consciousness is unclear. It has been previously discussed that coronaviruses are neurotropic viruses and that COVID-19 should not be considered an exception. The ACE_2 receptor, also found in neurons and glia, has been recognized as the major binding target for COVID-19. The endocytosis pathway is mainly the clathrin-dependent endocytosis pathway, previously recognized in SARS-CoV-1 infections and reaffirmed in COVID-19 infections [54]. Furthermore, epithelial cells of the choroid plexus have been found severely infected by COVID-19. Therefore, neuroinflammation with reactive astrogliosis and activation of microglia with possible disturbances in CSF production and circulation is a very likely mechanism (Jacob F., *et al*. 2020. Steardo L.., *et al*. 2020). An indication for this mechanism is that SARS-CoV-1 has been found in the cerebrum, known for its high density of neuroglia and host of the choroid plexus, and not in the cerebellum, where neuroglia is found in small amount [55,56]. In specific, the brainstem, which hosts the ascending reticular activating system enabling the state of consciousness, is severely infected by SARS-CoV-1 and MERS-CoV in rats (Steardo L., *et al*. 2020). Similar findings have been reported for COVID-19 of the olfactory nerve, the gyrus rectus and the brainstem in humans [57]. Therefore, the most likely pathway of brainstem infection with COVID-19 is through the olfactory nerve to the brainstem. This can occur even with very low viral doses in rats without respiratory symptoms [58]. Another possible direct pathway for CNS infection with COVID-19 is via compromisation of the blood-brain barrier due to systematic inflammation (Steardo L, 2020). However, more investigations of the mechanisms of COVID-19 affecting the brain are needed.

Seizures

Seizures occur as part of meningitis or encephalitis in patients diagnosed with Covid-19, whereas other patients developed episodic seizures, which rarely developed to focal status epilepticus. Seizures were noted to arise among patients with more severe SARS-CoV-2 infection and people of older age with medical comorbidities.

An early study from city of Wuhan, China, the center of the pandemic outbreak, noted that neurological involvement among patients (n = 214), at some degree, were far less than the respiratory symptoms. At this specific study the incidence of seizures, out of the more severe neurological sequelae, was estimated at 0.5% [59].

In another systematic review in a Spanish population during March 2020, 841 SARS-CoV-2 positive patients (blood test antibodies or swab throat sample rt-PCR) were hospitalized and studied. Among them, six patients (0.7%) developed seizures and none of them were complicated by status epilepticus. Out of these six patients, 66% occurred in severe stage disease (2 of them after intracranial hemorrhage). 3 patients among them had focal onset seizures, whereas the type of seizure was not related to the severity of the infection. We do not know the type of medication that was administered to these patients (Romero-Sánchez, C. M., 2020).

Also, in a retrospective multicenter study of 304 patients in China [60], only 2 patients (0.65%) were observed to develop seizure like events. None of them had previous history of epilepsy. The term "seizure-like events" here is used, as the first patient was diagnosed with acute anxiety disorder rather than epileptic seizure, while the second developed symptomatic seizures on the ground of metabolic disturbance. Both patients were treated properly (antipsychotics and diazepam, metabolic disturbance correction, respectively). Data from these studies are in accord, indicating that the total incidence of neurologic signs in SARS-CoV-2 positive patients range between approximately 35-50%, while specifically concerning seizures, the rate is below 1%.

Several recent case reports describe the occurrence of seizures in the context of SARS-CoV-2 infection: One of them outlines a 78-year-old female patient with a 2-year status free post encephalitic epilepsy, that presented to the emergency room with right eyelid and upper lid status epilepticus. The interesting fact with this patient was the first aid evaluation (alert and eupnoeic patient with normal body temperature). Only 14 hours after the status onset did she develop fever. She tested positive for SARS-CoV-2 (nasopharyngeal and oropharyngeal swap samples rt-PCR) [61].

There is also a report of meningitis/encephalitis associated with SARS-CoV2 infection accompanied by seizures. In this, a 24-year-old male with no travel history abroad, established disturbance of consciousness and general tonic-clonic seizures 9 days after the appearance of an influenza-like febrile syndrome. The radiologic exam indicated viral pneumonia and meningitis that was complicated with status epilepticus. The SARS-CoV-2 RNA was not found in the nasopharyngeal swab, although it was detected in the CSF (Moriguchi, T.., *et al*. 2020).

Also, a 35-year-old woman with headache and drug refractory seizures, is reported having total improvement after undergoing a surgical intervention. Magnetic Resonance Spectroscopy was suggestive of a high grade glioma rather than a non-neoplastic lesion, whereas encephalitis was verified histopathologically. She later mentioned having had flu like symptoms 2 weeks prior her CNS symptoms, and tested positive for SARS-CoV-2 [62].

There are 2 cases reported from an Ohio-based health system, mid-March 2020, describing 2 advanced-age patients with no known history of epileptic seizures prior to the SARS-Cov-2 infection, that developed focal seizures during their hospitalization (day 2 and 5 of hospitalization, respectively). The former patient developed upper extremity clonic activity and a decline in consciousness, while the latter had right eyelid and facial twitching that eventually progressed to focal status epilepticus. Both patients were found to be SARS-CoV-2 positive (nasopharyngeal swab PCR), were not tested on CSF, and had their seizures managed with levetiracetam [63].

Since the case number is limited, we can only speculate that seizures may be caused by the generalized poor condition, cytokine storm, or mesial temporal lobe involvement in severe COVID-19 patients.

Dizziness

Dizziness is a frequent neurological symptom of COVID-19, occurring in 7-9.4% of cases (Wang D., *et al*. 2020). In a study of 138 hospitalized patients, there was an increased probability of patients in the ICU (8/36 patients, 22.2%) feeling dizzy, more than those not in the ICU (5/102 patients, 4.9%) (P = 0.007).

Mao L.., *et al*. focused on the neurological symptoms of 214 patients with COVID-19 and found that the most popular one was dizziness (36 patients, 16.8%), second was headache (28 patients, 13.1%), and third was impaired consciousness (16 patients, 7.5%). The next most common include acute CVD (6 patients, 2.8%), ataxia (1 patient, 0.5%), and seizure (1 patient, 0.5%).

Cranial nerves

Olfactory and gustatory malfunction is a recurrent symptom of COVID-19 patients. Otolaryngologists and head-neck surgeons have to be aware of this symptom when diagnosing ageusia and nonspecific anosmia that came unexpectedly and is not related to rhinitis symptoms. Symptoms related to the cranial nerves have been observed (8.9% of cases), like hypogeusia, hyposmia, visual impairment, and neuralgia (Mao L.., *et al* 2020).

Anosmia-hyposmia and ageusia

Impairment of the smell and taste senses related to COVID-19 are thought to be rare by Chinese counterparts. One early study about the progression of the virus demonstrates that smell and taste dysfunction are initial symptoms of COVID-19, typically presenting themselves within the first five days of symptoms. Looking at the prevalence of neurological symptoms in 214 patients, Mao., *et al*. discovered anosmia in 11 (5.1%) and ageusia in 12 (5.6%) cases. Additionally, in 72 patients, the first symptom they noticed was ageusia and anosmia. As more is being learned about the virus and its progression, there is an increase in patients with chemosensitive malfunction, ranging from 19.4% to 88% in the above European study.

Taste dysfunction only was documented in 9 cases (12.5%) and olfactory disorder only was found in 14 patients (14.4%). 30 patients (41.7%) said that they had impairment in taste and olfaction. 44 patients (61.1%) mentioned having or that they had smell dysfunction when infected with COVID-19. Overall, 34 patients had complete anosmia, 8 had hyposmia, and 2 dysosmia (Vaira., *et al*.). 39 patients noticed taste malfunction, which was fully recovered in eight patients. 28 patients reported having full ageusia and 11 said they had varying levels of hypogeusia that was related to dysgeusia in seven patients (Vaira., *et al*.). The sense primarily altered was sweet for 23 patients and sour for 21 patients, though there was no obvious trend toward damage of one specific taste. Altogether, 73.6% of patients communicated having or having had chemo-sensitive disorders.

An additional study of olfaction revealed various levels of hyposmia in 60 patients and anosmia in two. Gustatory evaluation showed hypogeusia in 33 patients and full ageusia in one. The difference in chemo-sensitive recuperation was statistically significant and was observed based on age and time from the start of the clinical symptoms. At this European study by Vaira., *et al*. at the beginning of the assessment, most patients (66%, 35 patients) communicated a full improvement of chemo-sensitive functions. This report came less than five days in 19 cases and more than five days in the rest (16 cases). However, 18 patients (34%) describe a prolonged impairment of taste and smell.

However, the possibilities of a higher detection rate of olfactory dysfunction in patients diagnosed by certain sub-specialists, such as neurologists or otolaryngologists, cannot be completely excluded. For instance, the study done by otolaryngologists (Lechien JR.., *et al*. 2020) found olfactory/taste disorders in more than 80% of the patients.

Thus, olfactory and gustatory impairments are frequent observations in COVID-19 patients. Otolaryngologists, neurologists, and head-neck surgeons have to be aware of this symptom when seeing cases of ageusia and nonspecific anosmia that came suddenly and are not related to rhinitis symptoms.

Vision impairment

The infection from SARS-CoV-2 disturbs the vascular system, probably by immune-mediated reaction. Given that blocking of intravascular clotting is likely to be more obvious in smaller vascular areas, ophthalmological evaluation is especially crucial to assess the level of retinal vascularization damage in those who have recovered from COVID-19. The ophthalmologist will review possible impairments that the viral infection might have caused to the retina. It will be essential to connect the level of retinal damage with that of cerebrovascular and/or cognitive impairment. Every COVID-19 patients should be given the option of a full ophthalmology exam, consisting of visual acuity assessment, anterior segment and ocular fundus photograph, 3D optical coherence tomography (OCT), and OCT angiography (OCTA). OCTA shows the vascular report *in vivo* and does not use dye injections. Additionally, macula and optic nerve evaluations are done to measure the level of macula/optic nerve vascular damage. These analyses and looking in depth at the vascular system with OCTA technology might assess the participation of all retinal layers (Gemelli., *et al*. 2020).

Other cranial nerves

There was a documented case of bifacial weakness with paresthesia, which is a known subtype of Guillain-Barré syndrome and is identified by a quick progression of facial weakness and paresthesia without ataxia or other cranial neuropathies, which presented itself around the same time as a COVID-19 precursor.

A 50-year-old man had anosmia, ageusia, right internuclear ophthalmoparesis, right fascicular oculomotor palsy, ataxia, areflexia, albuminocytologic dissociation, and positive testing for anti-GD1b-immunoglobulin G antibody. Five days before, he had a cough, malaise, headache, low back pain, and fever. Similarly, A 39-year-old man had ageusia, bilateral abducens palsy, areflexia, and albuminocytologic dissociation. Three days before, he had diarrhea, a low fever, and poor overall condition [64].

Ataxia

In patients with severe COVID-19 symptoms, ataxia, seizures, stroke, and decreased level of consciousness were the most common. The first case of COVID-19-related acute cerebellitis was documented in a 47-year-old man. He had been experiencing fatigue, pain, and a cough in the week and a half leading up to his admittance, and by day three, had vertigo, headache, and ataxia. He did not have nausea, vomiting, tinnitus, or hearing loss associated with his vertigo, nor did he lose or change his sense of taste and smell. However, the ataxia and vertigo were severe enough that the interrupted his regular life. During the initial ten days, he was consuming only over-the-counter drugs, not consulting with a doctor. His overall past medical history was average. When examined, it was observed that he has an ataxic gait and mild dysarthria. Further evaluation showed impaired tandem gait, wide-based and ataxic gait, head titubation, mild truncal swaying while sitting on a bed, irregular quick alternating hand movements, mild dysarthria, and dysmetria in upper extremities (finger to nose) and lower extremities (heel to shin). For the eye movement exam, he showed hypermetric vertical and horizontal saccades with normal velocity, instability of visual fixation in the primary position, saccadic pursuit (saccade superimposed on a pursuit eye movement), loss of optokinetic nystagmus, impaired vestibular suppression response, and end gaze rotational nystagmus. He scored 14 out of 40 on an ataxia assessment scale (SARA). In all other regards the examinations were average. This patient had positive SARS-CoV-2 PCR in his cerebrospinal fluid, so given his acute cerebellitis as well, he was given lopinavir/ritonavir at 400/100 mg twice a day for two weeks. Throughout his stay in the hospital, steroids and IVIg were not administered, giving full credit to the antiviral therapy for clearing his symptoms. His PCR was rechecked from oropharyngeal and nasopharyngeal specimens ten days after the start of his treatment. He did not give consent for his CSF to be sampled. After two weeks of this treatment, he had improvement of his vertigo, and his SARA score went down five points, to 9 out of 40. After four weeks, he saw improvement in his ataxia, and his SARA score decreased even more, to 3 out of 40. In any patient who has ataxia or clinical symptoms similar to acute cerebellitis should be promptly diagnosed, specifically tested for SARS-CoV-2, and isolated to stop the spread of the disease.

Psychiatric disorders

While proceeding to next day, after beginning of this pandemic due to the COVID 19, medical community start to concern about mental health consequences beyond the main medical issues. Psychological issues are coming to the fore about patients with COVID 19 infection, health care workers and for the community. In this direction, Chevance., *et al*. in their review suggest that mental health workers should be prepared to face an emotional pandemic due to the COVID 19.

COVID-19 survivors have had traumatic experiences, not only because they had a serious virus, but because of the strangeness of their hospitalization. Persistent fever, pain, difficult breathing, and exhaustion made patients feel depressed and lose hope. In the intensive care unit, patients had an intense fear of dying. In general, in the hospital, patients were isolated because of the risk of spreading the virus. They remained alone for extended periods of time, shortening their visits with doctors and nurses, which only intensified their suffering and sparked feelings of loneliness. The fear that they were still contagious followed some patients out of the hospital. There was a great increase in risk of mental disorders, such as anxiety and post-traumatic stress disorders, because of these serious emotions and experiences. The isolation along with feeling lonely increase the chance of death, specifically suicide. Because of the aforementioned concerns, there is mental health support for the post-COVID-19 phase to inhibit the chance of serious psychiatric disorders in the future [65].

Mood disorders are an important aspect in mental health issues surrounding COVID 19. In a recent meta-analysis by Rojers and al, depressed mood was observed in acute illness (32.6%) as well as at post illness (10.5%). Similar percentages of depressive symptoms (around 35%) were also recorded in other studies (Vindegaard., *et al* 2000). Beyond the higher levels of depressive symptoms in patients with COVID 19 infection, authors of another review highlighted that patients with preexisting psychiatric disorders reported worsening their symptoms, and health care workers experienced depressive symptoms, psychological distress, anxiety and sleep disturbances (Vindegaard., *et al* 2000). Even more, some cases of steroid induced mania and psychosis have been described during the management of acute COVID 19 infection.

Delirium is an important clinical presentation of patients with COVID 19 infection. On the one hand confusion have been observed in 27.9% of such patients (Rogers JP, 2000). Possible pathophysiologic explanations of the conscious disturbances, like agitation and hallucinations, are the neuroinflammation process of the virus itself in brain, drugs withdrawal and drugs interactions (Vinde-

gaard., *et al*. 2000). On the other hand, hallucinations are connected with isolation in the literature and this differential diagnosis should be done during the management of such patients in the pandemic period (Chevance., *et al*. 2000).

Generalized anxiety disorder accounts for 35.1% of the public during the pandemic according to a cross sectional study (Vindegaard., *et al*. 2000). In the multivariate analysis of this study health workers, young age (>35 years) and prolonged time focusing on COVID 19 (more than 3 hours per day) were associated with anxiety and low quality of sleep. Sleep disorders and anxiety are connected in a vicious circle. Rogers., *et al*l in their meta-analysis reported percentages as 41.9% for insomnia and 35.7% for anxiety in patients with acute illness of COVID 19 and 12.1 and 12.3 respectively for post illness period. Another study, from China in the pick of the disease, showed a prevalence in general population of depression, anxiety and somatization as 47.1%, 31.9% and 45.9% respectively [66]. In one case severe anxiety lead to suicide attempt.

Suicidality is one of the most important aspects in the psychiatric view during pandemic [67]. Interestingly, in Japan a death after suicide was recorded even before any death due to the COVID 19 infection in this country (Rogers JP, 2000). In this case a 37 years old man who was in charge for isolated returnees suicide. Moreover, sleep disorders occurring during the pandemic period in a wide range of population, are recognized as strong risk factors for suicidal ideation, suicide attempts and suicidal death [68]. Suicidality was also recorded in 2 of 100 patients in a study during acute infection of COVID 19 (Rogers JP, 2000).

Interestingly, a range of 8% to 96,2% of patients with COVID 19 illness have been reported by several studies to had symptoms meeting post-traumatic stress disorder (PTSD) criteria (Ran., *et al*. 2000). Like anxiety, PTSD appears in patients with COVID 19 as well as in health care workers (Szcześniak., *et al*. 2000). Furthermore, patients with preexisting mental health problems, females, those with relatives suffering from COVID 19 and patients with other comorbidities had low psychological resilience and high risk for psychiatric disorders (Vindegaard., *et al*. 2000)whereas only few studies address the potential direct effect on mental health of SARS-CoV-2 and the neurotropic potential. Furthermore, the indirect effects of the pandemic on general mental health are of increasing concern, particularly since the SARS-CoV-1 epidemic (2002–2003.

Psychotic disorders are also concerning in the pandemic period. Reports from Italy [69,70], included six patients, with first episode of psychosis during the second month of the national lockdown, where the three of them had somatic delusion of been infected from COVID 19 although all were negative. Authors conclude that an intense psychosocial stress due to a fatal disease and national lockdown may be triggering a first brief episode of psychosis. Persecutory ideas were seen in 3.9% and 2% in acute and post-illness of COVID-19 respectively, and unspecified psychotic symptoms were seen more frequently (4.4%) in post-illness patients (Rogers., *et al*. 2000).

From a recent meta-analysis of studies published between January 1st and April 10th, 2020, occurrence of more severe psychiatric impairments including depression (29%), anxiety (34%) and post-traumatic stress disorder (34%) was observed in COVID19 patients along with mild symptoms (Rogers., *et al*. 2020).

Paterson., *et al* tells the story of a 55-year-old female coronavirus patient. Although she had no psychiatric illness history, she acted strange the day she left the hospital. She constantly took off her coat and put it back on and hallucinated, imaging monkeys and lions in her home. The hospital brought her back and she slowly got better with the help of antipsychotic medication.

Symptoms after COVID 19

Numerous studies on the short-term effects on COVID-19 patients have been published, however there is a large gap when it comes to long-term effects on those who have recovered from the acute phase of COVID-19. It is reasonable to believe that most recovered patients who had mild symptoms will not experience serious long-term complications and at some point, will completely recover. Additionally, no lasting complications were publicized for those who had moderate to severe symptoms and were in the hospital but did not require ventilation. However, those with severe symptoms who required ventilators should expect persistent complications and not a full recovery.

The strength of the virus in various parts of the body will determine what comes after the initial phase. While evaluating the patient after acute care, it is important to document the psychiatric and neurological symptoms that took place throughout the initial phase of the virus in order to track their continuation into the post-COVID-19 phase. Additionally, the later assessments must use a particular neuropsychological evaluation to measure cognitive

functions, specifically attention, memory, and language, and how they intersect with psycho-behavioral dimensions (Gemelli., *et al*. 2020).

A recent study found that in those who recovered from COVID-19, 87.4% reported the prolonging of at least 1 symptom, specifically fatigue and dyspnea [71]. Many individuals continued to report fatigue (53.1%), dyspnea (43.4%), joint pain, (27.3%) and chest pain (21.7%) assessed a mean of 60.3 (SD, 13.6) multiple days after their initial COVID-19 symptom. At the time of the evaluation, only 18 (12.6%) were free of any COVID-19-related symptoms, while 32% had 1 or 2 symptoms and 55% had 3 or more. A decrease in quality of life was observed among 44.1% of the patients in the above study.

COVID-19 patients who come to the hospital with pre-existing neurological disease, such as stroke, are more likely to experience impairments and increased rates of mortality.

It is possible that the virus will leave a small amount of the population with brain damage that will not be obvious until years later. We do not wish this to be true, although with a large-scale pandemic affecting most of the population, we must be aware of the possibility. Perhaps this occurred after the 1918 flu pandemic, when almost one million people seemed to have developed brain damage. Most research has concentrated on the initial, short-term phase of COVID-19, but it is crucial that long-term tracking take place to understand the lasting effects.

Conclusion

In the reality of the COVID-19 pandemic, it is fundamental to ensure that clinicians will be aware of the neurological and the mental health aspects and symptoms of COVID 19 infection and be able to manage them. For this propose telemedicine could be very helpful, including monitoring of suicide risk and psycho education strategies (Mengin., *et al*. 2000)submarines, prison. Moreover, enhanced education about the prevention, early detection and treatment of the neurological and psychological consequences of the pandemic in patients and health care professionals is vital. Arguably the most important step in reducing the spread of the virus is to quickly diagnose new cases. Thus, neurological experts, such as neurologists and psychiatrists, must know about the neurological symptoms of COVID-19 and not disregard novel findings. It is imperative that we create post-COVID-19 rehabilitation programs. We have witnessed the long-term effects that the virus has, both physically and cognitively, and they will require interventions.

Bibliography

1. Tsivgoulis G., *et al*. "Neurological manifestations and implications of COVID-19 pandemic. Version 2". *Therapeutic Advances in Neurological Disorders* 13 (2020): 1756286420932036.

2. Mao L., *et al*. "Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China". *JAMA Neurology* 77.6 (2020): 683.

3. Köhler-Forsberg O., *et al*. "Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: meta-analysis of clinical trials". *Acta Psychiatrica Scandinavica* 139.5 (2019): 404-419.

4. Bostanciklioglu M. "Severe acute respiratory syndrome coronavirus 2 is penetrating to dementia research". *Current Neurovascular Research* (2020).

5. Zhou Z., *et al*. "Understanding the neurotropic characteristics of SARS-CoV-2: from neurological manifestations of COVID-19 to potential neurotropic mechanisms". *Journal of Neurology* 26 (2020): 1-6.

6. Chen T., *et al*. "Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study". *BMJ* 368 (2020): m1091.

7. Ge J and Barnes NM. "Alterations in angiotensin AT1 and AT2 receptor subtype levels in brain regions from patients with neurodegenerative disorders". *European Journal of Pharmacology* 297.3 (1996): 299-306.

8. Yin C., *et al*. "Clinical analysis of multiple organ dysfunction syndrome in patients suffering from SARS". *Zhongguo weizhong bing ji jiu yi xue= Chinese critical care medicine= Zhongguo weizhongbing 'jijiuyixue* 16.11 (2004): 646-650.

9. Merkler AE., *et al*. "Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs Patients With Influenza". *JAMA Neurology* (2020).

10. Zhao H., *et al*. "Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence?". *Lancet Neurology* 19.5 (2020): 383-384.

11. Klok F., *et al*. "Incidence of thrombotic complications in critically ill ICU patients with COVID-19". *Thrombosis Research* 191 (2020): 145-147.

12. Kristoffersen ES., *et al*. "Effect of Covid-19 pandemic on stroke admission rates in a Norwegian population". *Acta Neurologica Scandinavica* 2020).

13. Zoghi A., *et al*. "A case of possible atypical demyelinating event of the central nervous system following COVID-19". *Multiple Sclerosis and Related Disorders* 44 (2020): 102324.

14. Ferrara F., *et al*. "Worldwide Recommendations and Therapies for Multiple Sclerosis: Are They Safe in the COVID-19 Pandemic Period?" *SN Comprehensive Clinical Medicine* 26 (2020): 1-2.

15. Paterson RW., *et al*. "UCL Queen Square National Hospital for Neurology and Neurosurgery COVID-19 Study Group. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings". *Brain* (2020): awaa240.

16. Argenziano MG., *et al*. "Characterization and clinical course of 1000 Patients with COVID-19 in New York: retrospective case series". *medRxiv* (2020).

17. Mi B., *et al*. "Characteristics and Early Prognosis of COVID-19 Infection in Fracture Patients". *Journal of Bone and Joint Surgery* 102.9 (2020): 750-758.

18. Du N., *et al*. "A case series describing the epidemiology and clinical characteristics of COVID-19 infection in Jilin Province". *Virulence* 11.1 (2020): 482-485.

19. Gupta N., *et al*. "Clinical and epidemiologic profile of the initial COVID-19 patients at a tertiary care centre in India". *Monaldi Archives for Chest Disease* 90.1 (2020).

20. Zhong ZF., *et al*. "Epidemiological and clinical characteristics of COVID-19 patients in Hengyang, Hunan Province, China". *World Journal of Clinical Cases* 8.12 (2020): 2554-2565.

21. Yang X., *et al*. "Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study". *The Lancet Respiratory Medicine* 8.5 (2020): 475-481.

22. Luo Y., *et al*. "Investigation of COVID-19-related symptoms based on factor analysis". *Annals of Palliative Medicine* 9.4 (2020): 1851-1858.

23. Xu XW., *et al*. "Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series". *BMJ* (2020): m606.

24. Kremer S., *et al*. "Neurologic and neuroimaging findings in COVID-19 patients: A retrospective multicenter study". *Neurology* (2020).

25. Ghweil A A., *et al*. "Characteristics, Outcomes and Indicators of Severity for COVID-19 Among Sample of ESNA Quarantine Hospital's Patients, Egypt: A Retrospective Study". *Infection and Drug Resistance* 13 (2020): 2375-2383.

26. Zayet S., *et al*. "Clinical features of COVID-19 and influenza: a comparative study on Nord Franche-Comte cluster". *Microbes and Infection* (2020).

27. Shi H., *et al*. "Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: A descriptive study". *The Lancet Infectious Diseases* 20.4 (2020): 425-434.

28. Tostmann A., *et al*. "Strong associations and moderate predictive value of early symptoms for SARS-CoV-2 test positivity among healthcare workers, the Netherlands, March 2020". *Eurosurveillance* 25.16 (2020).

29. Chen N., *et al*. "Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study". *The Lancet* 395.10223 (2020): 507-513.

30. Koh J., *et al*. "Epidemiological and Clinical Characteristics of Cases During the Early Phase of COVID-19 Pandemic: A Systematic Review and Meta-Analysis". *Frontiers in Medicine* 7 (2020).

31. Zhang X., *et al*. "Epidemiological, clinical characteristics of cases of SARS-CoV-2 infection with abnormal imaging findings". *International Journal of Infectious Diseases* 94 (2020): 81-87.

32. Jin X., *et al*. "Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms". *Gut* 69.6 (2020): 1002-1009.

33. Li J., *et al*. "Identification of Symptoms Prognostic of COVID-19 Severity: Multivariate Data Analysis of a Case Series in Henan Province". *Journal of Medical Internet Research* 22.6 (2020).

34. Lian JS., *et al*. "Comparison of epidemiological and clinical characteristics of COVID-19 patients with and without Wuhan exposure". *Journal of Zhejiang University-SCIENCE B* 21.5 (2020): 369-377.

35. Romero-Sánchez C M., *et al*. "Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry". *Neurology* (2020).

36. Guan W., *et al*. "Clinical Characteristics of Coronavirus Disease 2019 in China'. *New England Journal of Medicine* 382.18 (2020): 1708-1720.

37. Li L., *et al*. "COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis". *Journal of Medical Virology* 92.6 (2020): 577-583.

38. Lechien J R., *et al*. "Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019". *Journal of Internal Medicine* 288.3 (2020): 335-344.

39. Lapostolle F., *et al*. "Clinical features of 1487 COVID-19 patients with outpatient management in the Greater Paris: the COVID-call study". *Internal and Emergency Medicine* 15.5 (2020): 813-817.

40. Moro E., *et al*. "The international European Academy of Neurology survey on neurological symptoms in patients with COVID-19 infection". *European Journal of Neurology* 27.9 (2020): 1727-1737.

41. Zhu J., *et al*. "Clinical characteristics of 3062 COVID-19 patients: A meta-analysis". *Journal of Medical Virology* (2020).

42. Kumar A., *et al*. "Clinical Features of COVID-19 and Factors Associated with Severe Clinical Course: A Systematic Review and Meta-Analysis". *SSRN Electronic Journal* (2020).

43. Pinzon R T., *et al*. "Neurologic Characteristics in Coronavirus Disease 2019 (COVID-19): A Systematic Review and Meta-Analysis". *Frontiers in Neurology* (2020): 11.

44. Zhu J., *et al*. "Clinicopathological characteristics of 8697 patients with COVID-19 in China: a meta-analysis". *Family Medicine and Community Health* 8.2 (2020).

45. Abdullahi A., *et al*. "Neurological and Musculoskeletal Features of COVID-19: A Systematic Review and Meta-Analysis". *Frontiers in Neurology* (2020): 11.

46. Chen X., *et al*. "A systematic review of neurological symptoms and complications of COVID-19". *Journal of Neurology* (2020).

47. Nascimento I J., *et al*. "Novel Coronavirus Infection (COVID-19) in Humans: A Scoping Review and Meta-Analysis". *Journal of Clinical Medicine* 9.4 (2020): 941.

48. Nepal G., *et al*. "Neurological manifestations of COVID-19: a systematic review". *Critical Care* 24.1 (2020).

49. Chen N., *et al*. "Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study". *Lancet* 395.10223 (2020): 507-513.

50. Mardani M., *et al*. "COVID-19 infection recurrence presenting with meningoencephalitis". *New Microbes and New Infection* 37 (2020): 100732.

51. Duong L., *et al*. "Meningoencephalitis without respiratory failure in a young female patient with COVID-19 infection in Downtown Los Angeles, early April 2020". *Brain, Behavior, and Immunity* 87 (2020): 33.

52. Ye M., *et al*. "Encephalitis as a clinical manifestation of COVID-19. *Brain, Behavior, and Immunity* 88 (2020): 945-946.

53. Ghannam M., *et al*. "Neurological involvement of coronavirus disease 2019: a systematic review". *Journal of Neurology* (2020).

54. Sureda A., *et al*. "Endoplasmic reticulum as a potential therapeutic target for covid-19 infection management?" *European Journal of Pharmacology* 882 (2020): 173288.

55. Ding Y., *et al*. "Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways". *Journal of Pathology* 203.2 (2004): 622-630.

56. Azevedo FAC., *et al*. "Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain". *Journal of Compressive Neurology* 513.5 (2009): 532-541.

57. Bulfamante G., *et al*. "First ultrastructural autoptic findings of SARS -Cov-2 in olfactory pathways and brainstem". *Minerva Anesthesiology* 86.6 (2020): 678-679.

58. Li K., *et al*. "Middle East Respiratory Syndrome Coronavirus Causes Multiple Organ Damage and Lethal Disease in Mice Transgenic for Human Dipeptidyl Peptidase 4". *Journal of Infection Disease* 213.5 (2016): 712-722.

59. Whittaker A., *et al*. "Neurological Manifestations of COVID-19: A systematic review and current update". *Acta Neurologica Scandinavica* 142.1 (2020): 14-22.

60. Lu L., *et al*. "New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: A retrospective multicenter study". *Epilepsia* 61.6 (2020).

61. Vollono C., *et al*. "Focal status epilepticus as unique clinical feature of COVID-19: A case report". *Seizure* 78 (2020): 109-112.

62. Ibrahim E Efe., *et al*. "COVID-19–Associated Encephalitis Mimicking Glial Tumor". *World Neurosurgery* 140 (2020): 46-48.

63. Hepburn M., *et al*. "Acute Symptomatic Seizures in Critically Ill Patients with COVID-19: Is There an Association?" *Neurocritical Care* 28 (2020): 1-5.

64. Costello F and Dalakas MC. "Cranial neuropathies and COVID-19: Neurotropism and autoimmunity 95.5 (2020): 195-196.

65. Sani G., *et al*. "Mental health during and after the COVID-19 emergency in Italy". *Psychiatry Clinical Neuroscience* (2020).

66. Ran L., *et al*. "Psychological resilience, depression, anxiety, and somatization symptoms in response to COVID-19: A study of the general population in China at the peak of its epidemic". *Social Science and Medicine* 262 (2020): 113261.

67. Shigemura J., *et al*. "Public responses to the novel 2019 coronavirus (2019-nCoV) in Japan: Mental health consequences and target populations". *Psychiatry and Clinical Neurosciences* 74 (2020): 281-282.

68. Sher L. "COVID-19, anxiety, sleep disturbances and suicide". *Sleep Medicine* 70 (2020): 124.

69. Huang Y and Zhao N. "Generalized anxiety disorder, depressive symptoms and sleep quality during COVID-19 outbreak in China: a web-based cross-sectional survey". *Psychiatry Research* 288 (2020): 112954.

70. Brief Psychotic Disorder during the national lockdown in Italy: an emerging clinical phenomenon of the coronavirus pandemic | Schizophrenia Bulletin | Oxford Academic.

71. Carfì A., *et al*. "Persistent Symptoms in Patients After Acute COVID-19". *JAMA* 324.6 (2020): 603-605.