Type of the Paper (Systemic Review)

Impact of COVID 19 on neurological manifestations in Fayoum University Hospitals: Systemic Review

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Abstract:

Chinese health officials kept an eye on a cluster of pneumonia cases that occurred in the Chinese city of Wuhan (Hubei, China) in December 2019. The novel coronavirus severe acute respiratory syndrome coronavirus-2 pathogen, often referred to as COVID-19, was the cause of this. The goal of this review is to concentrate on the neurological manifestations of the 2019 coronavirus disease and to describe the existing published data as well as ongoing trials. Scopus, PubMed, and the Cochrane Library were searched from their inception until May of 2020 for any published papers using the terms "COVID-19" and "neurological disorders." To make sure no other clinical trials were overlooked, a separate search of Google Scholar was also conducted. The author examined the list of references of the research that was cited or relevant reviews that were recognized through the trial to make sure that the literature was sufficiently covered. If there were many publications on the same clinical trial, the most recent and thorough report was the one that was chosen. A search of all three databases yielded a total of 89 articles. Twenty-two full-text papers were reviewed for eligibility, and twelve were found to be ineligible. There were 290 patients reported to have neurological symptoms throughout all investigations. All central nervous system (CNS) signs, except headache, were more common in severe cases, according to the COVID-19 severity classification. Adults only participated in all of the included investigations. The neurological symptoms of the 2019 coronavirus disease should be studied because of the potential consequences they hold; however, many studies reveal that the psychosocial symptoms are far more common. It is still unknown from the research conducted so far whether or not brain infection is a subsequent symptom of COVID-19. However, if the brainstem were to become infected, it might disrupt normal breathing processes and throw the body out of balance.

Key words: COVID-19; Stroke; Insomnia; Neurological Manifestations.

1. Introduction

Millions of people could be killed by the 2019 coronavirus disease pandemic (COVID-19). On December 12, 2019, a novel coronavirus identified as severe acute respiratory syndrome coronavirus-2, or SARS-CoV-2, was initially detected in the country of China and has since rapidly spread throughout the rest of the world [1].

The SARS-coronavirus -2 virus is between 26 and 32 kilobases in length and is one of the Beta-coronavirus family. The RNA virus has a protective coat of a single-stranded, positive-sense RNA genome [2].

Two bat coronaviruses that are most similar to SARS share a common ancestor. Viruses contain 4 structural proteins: the envelope (E) protein, the spike (S), the nucleocapsid (N), and the membrane (M) [3].

The severe acute respiratory syndrome coronavirus-2, a cousin of COVID-19, enters human cells via binding to angiotensin-converting enzyme 2 (ACE2) with its spike protein. SARS-CoV-2 enters cells via angiotensin-converting enzyme 2, by recent investigations (4). ACE2 is found in many diverse tissues, including the brain and nerve cells [5]. The 2019 coronavirus disease can cause a wide spectrum of clinical presentations. The most common signs of the sickness are a high temperature, a cough, and difficulty breathing [6].

Clinical evidence from 2019 suggests that severe acute respiratory syndrome coronavirus-2 infects the CNS and, by extension, impacts pulmonary function. The respiratory center in the brainstem has been recognized as a main target of severe acute respiratory syndrome coronavirus-2, which causes a malfunction in the respiratory centre and severe respiratory distress simultaneously in individuals with the 2019 coronavirus illness [7]. Even though the vast majority of studies have the respiratory presentation of COVID-19, in light of the recent severe acute respiratory syndrome COVID-19 outbreak, the neurological aspects of this virus have become more apparent [4, 8].

The SARS-CoV-2 displays strong similarities in both genomic sequence and clinical symptoms with severe acute respiratory syndrome coronavirus-2, and MERS- coronavirus. The brain has been hypothesized to be a primary target of coronaviruses based on previous clinical and experimental data [3, 6]. In the early 2000s, these viruses were also shown to be present in the cerebrospinal fluid (commonly known as CSF) of both severe acute respiratory

syndrome and MERS individuals who were infected [8, 9].

The piriform, olfactory bulb, as well as basal ganglia (and lateral preoptic areas and ventral pallidum), infra-limbic cortices, and, in addition, midbrain (dorsal raphe) were also found to contain high concentrations of SARS-CoV virus antigen in infected patients [9-11].

The neurological symptoms and consequences experienced by 2019 coronavirus disease are not surprising in light of the similarities between severe acute respiratory syndrome coronavirus-two as well as other beta coronaviruses. A wide variety of neurological symptoms, from mild and non-specific (vomiting, nausea, headache, drowsiness, myalgia, and unsteady gait) to severe (meningitis, encephalitis, cerebral hemorrhage, and other neurological complications), have been reported by patients infected with novel coronaviruses. [12- 15]. Hematogenic route, retrograde neuronal transport, and anterograde neuronal transport have all been implicated as entry points for SARS-CoV-2 into the central nervous system [15–17].

The purpose of this review is to examine and synthesize the current research on neurological manifestations of coronaviruses.

2. Methods

During the process of preparing this review, we made sure to adhere to the principles outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [18].

2.1. Trial or study type

Articles that published the findings of non-randomized controlled trials, randomized controlled trials, case reports, retrospective studies, and case series of neurological symptoms in persons with COVID-19 were considered for inclusion. Cases with 2019 coronavirus disease who had been clinically or laboratory-diagnosed, as well as individuals who were hospitalized with neurological signs (with or without additional manifestations), were included in the study population. Patients could be of any age group or gender. People who already had primary neurological diseases that were complicated by coronaviruses were not allowed to get treatment.

There were two categories of neurological symptoms: central nervous

system symptoms like headache, dizziness, ataxia, encephalopathy, confusion, acute cerebrovascular disease, disturbed conscious level, meningo-radiculitis, myelopathy/ myelitis, pure meningitis, and seizure; in addition to peripheral nervous system (PNS) symptoms like loss of smell, taste, isolated cranial nerve impairment, vision, polyradiculopathy, nerve pain/neuropathic pain, Parenchymal lesions of the brain were included in the definition of encephalopathy. These lesions included stroke, vasculitis, CNS sarcoidosis, MS, and posterior reversible encephalopathy syndrome. Neuropathy comprises all types of peripheral involvement (mononeuritis multiplex, mononeuropathy, as well as polyneuropathy). Myopathy, polymyositis, myositis, dermatomyositis, also inclusion body myositis was all considered disorders of the muscles. Participants with myalgia/muscle discomfort but no weakening or neurophysiological diagnosis of myopathy/myositis were not considered.

Exclusion criteria

Excluded were research done in languages other than English, for which full-text publications were not available, on animals, as well as theses, conference presentations, and clinical trials still in progress. Pre-severe acute respiratory syndrome coronavirus-2 (that is, pre-December 2019) articles were not included.

2.2. Sources of information and search

Scopus, PubMed, and the Cochrane Library were searched from their respective establishment dates (January of 1996) to May of 2020 for any published papers including the terms " coronaviruses-19" and "neurological disorders." To make sure no more clinical trials were overlooked, an extra search was conducted using Google Scholar. The author checked the reference lists of the included studies and pertinent reviews found through the search to guarantee comprehensive coverage of the literature. In cases where the same clinical study was documented in multiple publications, however, only the most up-to-date and thorough report was considered for this analysis.

3. Results
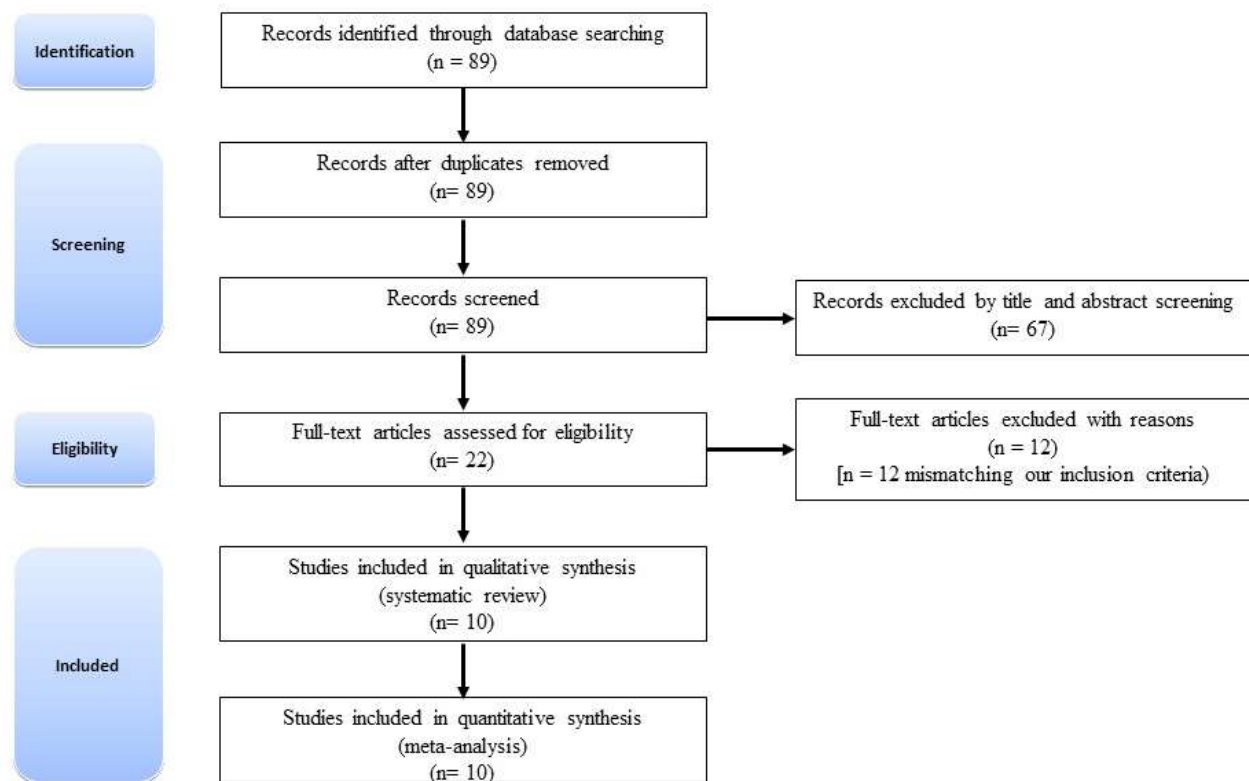
Figure 1: PRISMA Flow diagram of search process.

A search of all three databases yielded a total of 89 articles. Twenty-two full-text papers were reviewed for eligibility, and twelve were found to be ineligible. There were 290 patients reported to have neurological symptoms throughout all investigations. While headaches were reported by most patients, dizziness was the most often reported neurological symptom (11.9%). According to COVID-19, neurological symptoms were classified as either (1) mild or (2) severe, with all CNS symptoms being more common in severe cases with the exception of headache, which was more common in mild individuals. Adults only were used in all of the included investigations. Participants' demographics across the involved trials are described in **Table 1**.

Table 1. Characters of the included studies.

Authors	Year	Country	Type of study	Age/Gender	Manifestation	Presentation
Moriguchi et al. [19]	2020	Japan	Case report	24/ Male	Encephalitis	Headache, fever, fatigue.
Poyiadji et al. [20]	2020	Detroit	Case report	54/Female	Encephalitis	Cough, fever, altered mental status, headache
Gane et al. [21]	2020	United Kingdom	Case series	31-50/ Males (8) and Females (3)	Anosmia	Hyposmia, headache, fatigue
Eliezer et al. [22]	2020	France	Case report	40 years female	Anosmia	Isolated Anosmia
Klopfenstein et al. [23]	2020	France	Retrospective study	47±16/ Males (33%) and Females (67%)	Anosmia, 37% hospitalized	Anosmia (54/114)
Gutiérrez-Ortiz et al. [24]	2020	Spain.	Case report	50/ Male 39/ Male	Guillian barre syndrome	Diplopia after having fever, diarrhea, ageusia
Avula et al. [25]	2020	United status	Case series	73-88/ Male (1) and Females (3)	Acute cerebro-vascular disease.	Four patients presented with severe stroke
Mao et al. [26]	2019	China	Retrospective, observational case series.	52.7±15.5/ Males (40.7%) and Females (59.3%)	Acute cerebrovascular disease.	Ischemic stroke (5), hemorrhagic stroke (1).
Duong et al. [27]	2020	United States.	Case report	41/ Female	Viral meningitis	Headache, fatigue, seizure

4. Discussion

The newly discovered coronavirus, sometimes referred to as SARS coronavirus 2, is the cause of the new public health pandemic known as the 2019 coronavirus disease. An

outbreak of a novel virus in Wuhan, China, in December 2019 (COVID-19) [28] quickly became a global pandemic and quickly spread to many other nations [29]. WHO has called this a global health emergency. On April 11, 2020, World Metre data showed that the United States had the highest number of infected people, with over half a million, subsequently followed by Spain and Italy. There's been no slowdown in the virus's spread, and that, along with the draconian lockdown measures, is a major cause for alarm. Fever, Shortness of breath, and cough have been the most commonly observed signs since the outbreak began, but recently, additional symptoms have emerged. These may be the result of sequelae or the virus itself. Many neurological symptoms, from headaches to encephalitis, have been documented in people with COVID-19 [30].

Pilotto et al. stated that a man in his 60s conveyed a serious disturbance in his state of awareness. The patient was diagnosed with encephalopathy, and tests in the laboratory revealed that his level of D-dimer was elevated. The study of the CSF showed that there was a slight rise in the number of lymphocytes, and there was also an increase in the number of proteins in the CSF [31].

A previous case report of a male patient aged 74 years old who tested positive for 2019 coronavirus disease was found to have encephalopathy [32]. The CT scan of the skull did not reveal any acute anomalies, and the findings of the EEG were in line with a diagnosis of encephalopathy as well as focal dysfunction in the left temporal lobe. Despite this, the examination of the CSF was normal.

In a retrospective trial performed at a single hospital, a total of 221 coronaviruses -19 cases were investigated to determine whether or not they presented with new onset acute cerebrovascular disease (CVD). Thirteen members in the cohort displayed detectable symptoms of cerebrovascular illness. People who had cardiovascular disease tended to be older and were more likely to have a number of risk factors than those who did not have cardiovascular disease. These risk factors included diabetes, hypertension, as well as an elevated C-reactive protein level [33].

Lau et al. indicated that a 32-year-old pregnant lady presenting with myalgia may have had severe acute respiratory syndrome COVID-19 involvement in her central nervous system. The patient's generalized convulsions were most likely brought on by the CNS illness [34].

Another large case series reviewed the clinical parameters of 1099 COVID-19 patients and discovered that 13.6% of them experienced mild neurological symptoms, including

headaches, and 14.9% experienced mild myalgias [35].

Ramanathan et al. anticipated that individuals with MS who receive modest immunosuppressive medication may be at higher risk for developing serious 2019 coronavirus disease problems [36].

Lechien et al. evaluated olfactory and gustatory disorders that occurred in a total of 417 individuals who had mild to significant COVID-19. Out of 417 individuals, 357 (85.6%) experienced olfactory impairment; of these, 284 (79.6%) demonstrated anosmia as well as 73 (20.4%) hyposmia [37]. Also, among these patients, 32.4% were parosmic, and 12.6% were phantom. Anosmia was also reported in the papers that were included in our systematic review [21-23].

Poyiadji et al. SARS-Cov-2 nucleic acid identification in a nasopharyngeal swab confirmed the diagnosis of 2019 coronavirus disease in a 50-year-old female with a 3-day history of fever, cough, and altered mental status [38]. Bacteria, herpes simplex virus types 1 and 2, varicella-zoster virus, and West Nile virus were all found to be absent from her cerebrospinal fluid sample. Medial thalamic hypoattenuation was found on both sides of the brain on a non-contrast CT scan of the head, although the angiography and venography showed no abnormalities. Magnetic resonance imaging indicated hemorrhagic ring-enhancing lesions in the medial temporal lobes, bilateral thalami, as well as sub insular regions, indicating acute necrotizing encephalitis. A case study suggests that severe acute respiratory syndrome coronavirus-2 can cause encephalitis. Gutiérrez-Ortiz et al., who was the first to demonstrate that infection with SARS-SARS-coronaviruses -2 is associated with Miller-Fisher syndrome, a form of the Guillain-Barré illness [24]. A man in his 50s who had a history of coughing, fever, malaise, headache, low back pain, as well as altered perceptions of smell and taste reported perioral numbness, double vision, and ataxia. He also had a history of these symptoms over the previous five days. It was discovered that the patient suffered from right fascicular oculomotor palsy in addition to right internuclear ophthalmospasms. The patient had an elevated level of GD1b-IgG antibodies, as shown by the test. An oropharyngeal swab was tested for severe acute respiratory syndrome coronavirus-2 using real-time reverse transcriptase polymerase chain reaction, and the results came back positive. His MRI of the brain, chest X-ray and CSF examination all came out clean. Miller-Fisher syndrome was the diagnosis given to the patient. He was treated with intravenous immunoglobulin. Three days after experiencing diarrhea, fever, and ageusia,

another patient arrived with diplopia. A bilateral 20/25 visual acuity and bilateral abducens palsy were found during the eye exam. Oropharyngeal swabs tested positive for SARS- coronaviruses-2 in a real-time reverse transcriptase polymerase chain reaction. His chest X-ray, MRI of the brain, and CSF examination all came out clean. Polyneuritis cranial is was diagnosed in this patient.

Wu et al. have proposed that the brain system is involved as well (viral encephalitis), joining respiratory failure as well as systemic illness [39]. Another case report presented a young female patient in Downtown Los Angeles with a COVID-19 infection who displayed meningoencephalitis without respiratory failure in early April 2020 [27]. By 2020, researchers will have seen a 2019 coronavirus disease infection manifest as a case of meningoencephalitis without any respiratory symptoms.

A review by Jin et al. reported that more than a third of 2019 coronavirus disease patients had some form of neurological distress [40].

Researchers looked back on the cases that involved three male patients aged 45–75 who were diagnosed with severe neurologic conditions, including changed level of consciousness (from confusion to coma), ataxia,

and focal motor impairment, in a retrospective study conducted in Saudi Arabia [41].

Strengths and limitations of the review

One useful aspect of this analysis is that it highlights the areas where further research is needed to better understand the neurological manifestations of COVID-19. Second, this assessment incorporates all relevant publications published between the issue's start in December 2019 and May 2020. Third, it can be used as a template for research into the neurological symptoms of COVID-19 persons as well as how to best treat them in the future. Moreover, the search and summary of ongoing trials with neurological manifestations in patients with this disease were incorporated into the project as a whole.

Research on this issue has important limits that should be acknowledged. To begin, there is a wide discrepancy across research in terms of the samples, methods, and outcomes. Second, there is a lack of specialized scales or scores to evaluate neurological manifestations or diseases, despite their frequent reporting alongside other symptoms. Third, only observational studies were used to determine the frequency of neurological manifestations because this information is not available from the vast majority of research (in terms of sheer numbers) that describes neurological

manifestations. Fourth, no research has reported a specialized treatment for neurological symptoms in patients with 2019 coronavirus disease. The fifth limitation is that, with the exception of a small trial, all participants were adults. Lastly, another drawback is the absence of a period of neurological manifestations, as, it is now recognized that some individuals continue to have symptoms for a reasonably long-time following clearance of their COVID-19 symptoms.

In addition, the majority of the research papers considered in the current systematic review were case series, case reports, as well as observational studies, and they had a small sample size of individuals with neurological signs of 2019 coronavirus disease.

Implications for future research

In order to have an improved understanding of the spectrum of neurological symptoms and the prognosis and mortality rates of COVID-19 patients, more appropriate RCTs need to be undertaken in future research. In addition, more research is needed to describe the full range of neurological signs seen in children with 2019 coronavirus disease. Neurological problems in post-COVID-19 individuals must be monitored for extended periods of time. The creation of an international consensus and guidelines for the effective care of neurological manifestations in 2019 coronavirus disease patients requires more research into the prevalence of these symptoms.

Conclusions

The aim of this research effort was to compile and synthesize the current research on the neurological symptoms of the 2019 coronavirus disease. Individuals with coronavirus disease -19 and neurological symptoms are required to be evaluated with an in-depth history and neurological examination performed by experienced neurologists.

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