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## Systemic review of CNS involvement and its manifestations in SARS-CoV2 positive patients



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### ABSTRACT

Coronavirus is known to cause various systemic infections both in human and animal which are mostly mild in nature. However, recent years have seen major pandemics caused by coronavirus which are very invasive and virulent in nature. The recent SARS-CoV2 is a new addition to this list of coronavirus pandemics. So the present study was done to systematically review the CNS involvement and its manifestations in SARS-CoV2 positive patients. Systemic review of article published between 1st Dec 2019 to 31st July 2020 searched through web-based database of MEDLINE (Pubmed) and Google scholar using following keywords "COVID -19" OR "CORONAVIRUS" OR "SARS-CoV2" AND "NEUROLOGICAL" OR "CNS" OR "BRAIN". Using the steps of systemic review eight article were selected for qualitative analysis. Majority of these article were reporting neurological symptoms among patients admitted in different wards along with others general symptoms. None of the study was specifically devoted to study the neurological manifestations and complications in SARS-CoV2 positive patients. The present study concludes that there is a scarcity of good quality research which attempts to establish the role of SARS-CoV2 infection in CNS and its manifestations. However, there are evidences that CNS involvement is present in majority of the patients. Proper documentation of these involvement and identification of these into mild, moderate and severe infection will help in early identification and treatment of these patients.

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### Contents

|   |     |
|---|-----|
| Introduction .....                                  | 735 |
| Material and methods .....                          | 735 |
| Results .....                                       | 735 |
| Discussion .....                                    | 735 |
| Mechanism of COVID-19 infection .....               | 735 |
| Long Hauler syndrome .....                          | 736 |
| Clinical manifestations in COVID-19 infection ..... | 736 |
| Viral encephalitis .....                            | 736 |
| Acute cerebrovascular accidents .....               | 737 |
| Infectious toxic encephalopathy .....               | 737 |
| Scope of future research .....                      | 737 |
| Conclusion .....                                    | 738 |
| Funding .....                                       | 738 |
| Competing interests .....                           | 738 |
| Ethical approval .....                              | 738 |
| References .....                                    | 738 |

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## Introduction

Human civilization has seen various pandemics ever since the history has recorded such incidences like Antonine Plague (165AD), Plague of Justinian (541–542 AD), Black Death (1346–1353 AD) etc [1]. Recent addition to this list of deadliest pandemics is COVID19 caused by Coronavirus.

Coronavirus is known to cause various systemic infection in both humans and animals majority of which are mild and self-limiting [2]. However, recent years have seen few of the severe forms of Coronavirus infections causing wide scale pandemics i.e. Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV) [3,4]. Most recent pandemics caused by Corona Virus is COVID-19. Due to its resemblance with the SARS, both in terms of clinical symptoms and the fact that both share same receptors, Angiotensin Converting Enzyme-2(ACE-2), it was named as SARS-CoV2 in February. However, World Health Organization (WHO) has renamed it as Corona virus Disease 2019 (COVID-19) [5].

Corona virus infection are known to be invasive in nature with its primary target being the lower respiratory tract cells, thus presenting with the symptoms of Lower respiratory infections leading to severe acute respiratory distress syndrome. In the initial incubation period, virus replicate in the mucosal cells located in the peripheral lung field. In the clinical phase when the virus load crosses the critical level, lung damage take place leading to fever, cough and shortness of breath. The virus also has potential to invade neurological tissue [6]. There are three probable route for the neuronal invasion namely:- Direct Inoculation, Blood circulation pathway and Neuronal pathway via a olfactory bulb. However, most probable route of infection is thought to be through olfactory bulb, causing inflammation and demyelination [5]. In the present study we will discuss the Nervous System involvement and its manifestation in COVID-19 patients.

## Material and methods

The present study was conducted according to the Preferred Reporting Item for Systemic Review and Meta Analysis (PRISMA) guidelines. Electronic database Medline (Pubmed) and Google Scholar were searched systematically for published articles from 1st Dec 2019 to 31st July 2020 using following keywords: “COVID-19” OR “CORONAVIRUS DISEASE” OR “SARS-CoV2” AND “NEUROLOGICAL” OR “CNS MANIFESTATIONS” OR “BRAIN”. The authors also searched references included in the selected articles to ensure sufficient literature to be available for review.

Authors 1st listed all the articles searched using electronic database-Medline and Google Scholar and from references of the selected articles. Only articles whose main text are available in English language were included in the study. After the listing, authors screened the articles based on the title and abstract of the article. In the 1st step, a total of 180 article were listed. Out of this, 97 articles were removed as their title did not match with the study objectives. 26 articles were further excluded because their main texts were not available in English language.

In the second step authors retrieved the full text of the short-listed article of the 1st step. Full text of the selected articles were reviewed first for the objectives of the study, study methodology, data collection process and limitations of the study. Thus, 57 out of shortlisted in the 1st step, full text of 54 articles were retrieved for further review. Full text of three articles could not be retrieved as they were not available for review at the time of writing the paper. Out of remaining 54 articles, 22 articles were excluded as they were duplicate articles. 11 articles were further excluded as their data collection process were not appropriate or dubious. Thus a final

list of 21 articles was prepared and following information were extracted from the selected studies: study design, main result and limitations of study (Fig. 1).

## Results

An extensive literature search was conducted through web-based system. A total of 180 article were identified through data search engines, Pubmed and Google scholar. However, after thorough screening only twenty one articles were selected for Qualitative analysis. On doing further qualitative analysis of these articles, it was noted in study that as high as 36.4% of covid-19 positive patients develop central neurological involvement [6]. Most common central nervous symptoms noted was headache and most common peripheral nervous symptom noted were anomia and dysgeusia. Another is correspondence which state that 14% of the ICU patients having corona infection develops neurological complication [7]. Beside these COVID-19 can present with variety of neurological manifestations like Guillain-Barré syndrome, Miller-Fisher syndrome etc. it was also reported that some COVID-19 positive patients may present with variety of non pulmonary symptoms. Also some case reports are also available which suggest positive CSF findings in COVID-19. One of the case reports also suggest EEG changes in corona positive [9] (Table 1).

## Discussion

It is noted in the present study that neurological manifestations are common in current COVID-19 positive pandemic. Corona virus are commonly found in both human and animals, but occasionally it cross the species barrier and cause serious pandemics and latest pandemic is an example of this crossing over. It has a huge on the society financial and non financial terms [2,28].

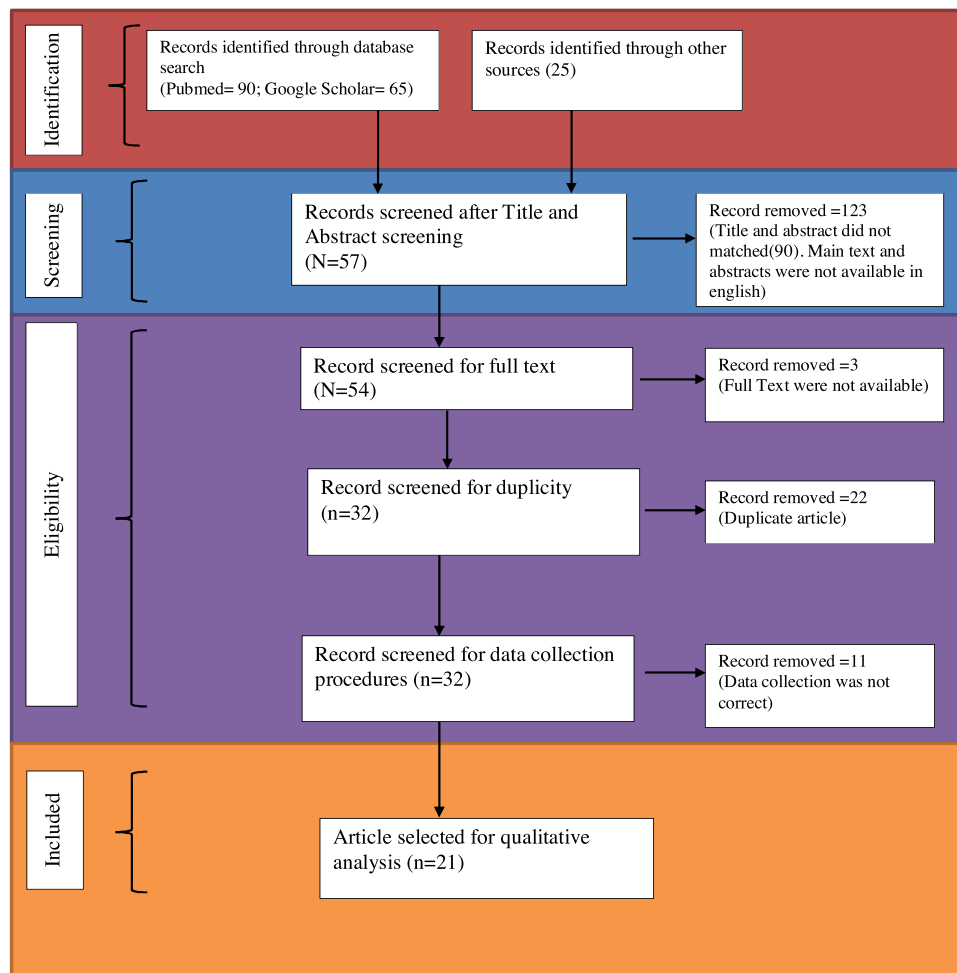
On doing qualitative analysis of the finalized articles, it was noted that there is scarcity of specific studies dedicated to study neurological involvement in COVID-19 patients and to established its association and the time line of neurological involvement in COVID-19 patients. Till then the findings of previous coronavirus pandemics can also be safely applied on the current SARS-CoV2 pandemic [29]. In 2003, SARS-CoV epidemic, patients with neurological manifestation had their CSF positive for the virus [3]. In study of patients suffering for MERS, neurological manifestation was also reported in few patients [30,31]. So, it's quite imperative to presume that the current pandemic will also have patients presenting with different neurological manifestations. Some of these manifestations will be specific like cerebrovascular accidents, seizures, meningitis, encephalitis whereas majority will have nonspecific symptoms like confusion, dizziness, headache, myalgia.

Studies done using retrospective data analysis of COVID-19 patients has shown that patients may have few symptoms of central nervous system involvement like headache, confusion, dizziness, and cerebrovascular accidents [7–13,17,20,22,23]. Symptoms like loss of taste and smell are signs of peripheral nervous system involvement [26]. However some patients may present with few symptom complexes like Guillain-Barré syndrome, Miller-Fisher syndrome etc [18,19].

## Mechanism of COVID-19 infection

Various mechanism has been proposed for the neuronal damages in COVID-19 patients like direct infection injuries, hypoxic injuries and immune mediated.

Direct injuries mostly take place through direct seeding of the virus into the neuronal tissue through blood circulation or via a olfactory nerve pathways. Direct seeding of the virus lead to



**Fig. 1.** Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram for the study.

viral encephalitis. Entry of virus is the most suggested pathway by different researchers. Mouse Hepatitis Virus model also support this hypothesis [32,33]. Virus migrate through sensory or motor neurons in both anterograde or retrograde directions through neuronal proteins, dynein and kinesin. Entry of the virus through olfactory nerve pathway take place in early phase of the infection. There are studies which indicate that patients present first with neurological symptoms are later found to be COVID-19 positive [34].

CNS involvement mostly take place in the second week of the infection due to hypoxic injuries. Thus leading to decrease oxygen saturation in the blood, this further lead to anaerobic metabolism in the mitochondria of the brain cells and accumulation of the acid in the neuronal tissues resulting in cerebral vasodilation, swelling of brain cells, interstitial edema, obstruction to blood flow leading to ischemia which result in headache and dizziness [35]. In severe cases, there is a raised intracranial tension which result in drowsiness, bulbar conjunctival edema and even coma. In patients who are prone to cerebrovascular accidents, hypoxia result in cerebral stroke via a release of cytokine storms which mostly happen in second week. Is through immune mediation [36].

Another mechanism related to the CNS manifestation. Persistence of the virus in the neuronal tissue and their ability to infect macrophages, microglia and astrocytes result in release of large quantities of proinflammatory cytokines like IL-2, IL-5, IL-6 and TNF- $\alpha$ . These cytokines are important for the cytokine storms and are directly correlated with the severity of the infection [37].

### Long Hauler syndrome

Recent months have seen some cases of COVID-19 being progressed to Chronic COVID Syndrome which have been referred to as Long Hauler syndrome in the updated literature [38,39]. Though the exact mechanism of this progression is still unknown, it is hypothesized that incomplete removal of the viral antigen plays a key role in its development. Incomplete removal of the viral antigen could be due to defective immune response or due to presence of specific HLA subtype. Therefore, persons with Chronic COVID Syndrome with Long Hauler should be screened to identify HLA subtype associated with the chronic progression of the disease.

Similar reasons have also been suggested for the asymptomatic patients who does not develop the disease but still continue to spread the disease.

### Clinical manifestations in COVID-19 infection

#### Viral encephalitis

Most cases present with headache, fever, vomiting and convulsions. In a case report by Xiang et al., reported a case of viral encephalitis with positive CSF for viral protein [12]. However, in a case report by Saiegh et al., reported two COVID 19 positive patients with neurological manifestations but their CSF were not positive for the viral protein [14]. This indicate that there is scope for future studies to confute or refute the presence of viral encephalitis due to COVID 19 infections. In addition to this, hemorrhagic

**Table 1**  
Studies and neurological manifestation included in this study.

| S. No | Author                      | Methodology                                     | Clinical manifestations  | Limitations  | Level of evidence |
|-------|-----------------------------|---|--|--|-------------------|
| 1     | Mao et al. [7]              | Retrospective analysis of 214 admitted patients | Dizziness (17%), headache (13%) impaired consciousness (7%), cerebrovascular accident (3%) | No CSF analysis, no EEG study  | Level 4           |
| 2     | Li et al. [8]               | Retrospective analysis of 221 patients          | Cerebrovascular accident was reported in 2.8% of patients                                  | No other neurological manifestation was reported                     | Level 4           |
| 3     | Huang et al. [9]            | Prospective study of lab confirmed patients     | Headache (8%)  | Not specifically designed for study of neurological manifestations   | Level 2           |
| 4     | Helm et al. [10]            | Retrospective study of 58 ICU admitted patients | 84% of the patient had neurological signs, agitation was present in 69% of the patients    | Only give details of severely ill ICU patients                       | Level 4           |
| 5     | Wang [112]                  | Retrospective study of 138 patients             | Dizziness (9%), headache (7%)  | Not specifically designed for study of neurological manifestations   | Level 4           |
| 6     | Yang et al. [12]            | Retrospective study of 52 patients              | Headache (6%)  | Not specifically designed for study of neurological manifestations   | Level 4           |
| 7     | Chem et al. [13]            | Retrospective study of 99 patients              | Confusion (9%), headache (8%)  | Not specifically designed for study of neurological manifestations   | Level 4           |
| 8     | Saiegh et al. [14]          | Case series of two patients                     | Both patients have neurological complications but non have viral RNA in the CSF            | Very small sample. Not correlate it with the severity of the disease | Level 4           |
| 9     | Beach et al. [15]           | Case report                                     | Case report on delirium in single patient  | Single case  | Level 4           |
| 10    | Xiang et al. [16]           | Case report                                     | Case report of Viral Encephalitis  | Single case  | Level 4           |
| 11    | Xu et al. [17]              | Case series                                     | Headache (34%)   | 62 cases   | Level 4           |
| 12    | Toscano et al. [18]         | Case report                                     | Guillain–Barré syndrome  | 4 cases  | Level 4           |
| 13    | Gutiérrez-Ortiz et al. [19] | Case report                                     | Miller Fisher syndrome and polyneuritis cranialis  | 2 cases  | Level 4           |
| 14    | Oxley et al. [20]           | Case series                                     | Stroke   | 5 cases  | Level 4           |
| 15    | Lee et al. [21]             | Cross sectional study                           | Anosmia and ageusia (15.3%)  | 3191 case  | Level 3           |
| 16    | Guan et al. [22]            | Retrospective analysis                          | Headache 13.4%   | 1099 cases   | Level 3           |
| 17    | Qian et al. [23]            | Retrospective analysis                          | Headache (7%), myalgia (5%)  | 91 cases   | Level 3           |
| 18    | Moriguchi et al. [24]       | Case report                                     | Meningitis/encephalitis  | Single case  | Level 4           |
| 19    | Bernard-Valnet et al. [25]  | Case report                                     | meningo-encephalitis   | Two patients   | Level 4           |
| 20    | Lechien et al. [26]         | Cross sectional studies                         | Olfactory(85% (and gustatory (88%) dysfunctions,   | 417 patients   | Level 3           |
| 21    | Fara et al. [27]            | Case report                                     | Macro thrombus and stroke  | One patient  | Level 4           |

posterior reversible encephalopathy syndrome, and acute necrotizing encephalopathy, including the brainstem and basal ganglia, have been described in case reports. It was also noted that there is a scarcity of literature showing which area of CNS specifically involved in COVID-19 and what are its signs.

#### Acute cerebrovascular accidents

Data from the various studies shown that there is a release of large amounts of cytokines from glial cells leading to cytokine storm [36]. Thus, patients with severe infection of SARS CoV2 infection are independent risk factors for the cerebrovascular accidents. Majority of these cerebrovascular accident are hemorrhagic / ischemic in nature. Elevated D dimer assay can be a guiding point for early identification of case which are at risk for developing signs of cerebrovascular accidents [40]. Studies conducted on COVID 19 positive patients in New York reported that majority of the patients are dying due to stroke in their early adulthood [41].

#### Infectious toxic encephalopathy

Infection toxic encephalopathy result from either systemic toxemia, metabolic derangement or hypoxia developed during the process of disease progression. Patients during their early course may present with headache, dysphoria and delirium. Seriously affected patients may develop loss of consciousness, coma or paralysis [42–44]. As the COVID -19 positive patients develop severe hypoxia during the course of the disease, they are prone to Infectious Toxic Encephalopathy (Guo et al.) [35]. This is fur-

ther supported by the autopsy finding of COVID-19 patients which shows signs of cerebral edema in brain tissues (Xu et al.) [44].

Neurological damages can be classified into temporary or permanent neurological damages. Majority of the patients may present with the symptoms of temporary damages in the form of brain fog, confusion, stiffness of limbs etc which may resolve as the disease progress. However, some may present with symptoms of permanent damages like decline in the cognitive function etc. especially in patients with Chronic COVID Syndrome with Long Hauler. Majority of these patients have chronic low grade inflammation in the neuronal tissue resulting in the loss of neuronal and glial cells which are responsible for the normal functioning of the nervous system. Another mechanism that has been proposed for the permanent damage has been the loss of above cells due to budding of new virion in them.

#### Scope of future research

Present pandemic has shown that there is limited information available as far as the pathophysiology of the disease is concern. It provides lot of opportunity for future research. Major areas where dedicated research required are:

- At molecular level to understand the mechanism of the disease involvement and its progression. Research is required to understand why some people develop the disease and while some do



not. We also need to understand why in some person the rate of disease progression is very fast while in some it is not.

- At community level to understand what are the long term sequelae in the post covid patients. This will help to get more precise definition of various terminologies like Long Hauler syndrome etc.

## Conclusion

The present study concludes that there is a scarcity of good quality research which specifically focus on neurological involvements in COVID19 patients. Also, the present study concludes that there is enough evidence to prove that SARS-CoV2 infection affect neurological tissues both in central and peripheral nervous system. Various mechanisms are proposed to explain the pathophysiology of neurological manifestations in COVID 19 positive patients which need to be established and verified. This should be supplemented with Biochemical and Electro-physiological studies.

The authors of the study also concludes that there is an urgent need to focus on the chronology of the CNS involvement and its syndromic management as establishing the chronology of the disease will help in early identification of the disease. This will help in effective treatment and reduction in the severity of the disease.

However, the present study also concludes that some patients, especially those with severe infection, may have clinical and subclinical neurological manifestation which can be assign to impaired electrolyte and metabolic derangement. This should also be considered while evaluating patients with neurological manifestations.

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## Ethical approval

Not required.

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