nCoV-2019 infection induces neurological outcome and manifestation, linking its historical ancestor SARS-CoV & MERS-CoV: A systematic review and meta-analysis

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Systematic Review

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Abstract

Importance: The first systematic review and meta-analysis to help clinician to identify early the sign and symptoms of neurological manifestation in COVID-19 positive patients which further help in early management of patients.

Objective: Present systematic review and meta-analysis aimed to discuss the prevalence of neurological involvement of the 2019-nCoV patients and assess the symptomatic trend of events as compared to the 2002 “SARS” and 2012 “MERS” pandemics.

Methods: The articles were systematically screened through several search engine and databases. The articles published or in preprint were included in the study till 15th May 2020. The systematic review done as per the published literatures which included 31 cross sectional, observational studies and case reports which revealed neural sign and symptoms in SARS-COV-2 disease. For meta-analysis, we included 09 observational and cross sectional studies which included COVID-19 positive patients and assessed the predominance of various neurological sign and symptoms in COVID-19 patients relation to SARS-2002 and MERS-2012. Data were analyzed by using the “*MedCalc* Statistical Software version 19.2.6 and reported as pooled prevalence. Heterogeneity was investigated (standard I^2 test).

Results: We have collected and screened about a total 2615 articles, finally we have included 31 articles for the systematic review and 09 for meta-analysis as per the inclusion/exclusion criteria. The analysis was made as per the prevalence rate of neurological symptoms during the COVID-19 positive patients. The cumulative neurological outcome of SARS-2002 and MERS-2012 was assessed to get the trends which is next tried to correlate the events with the current pandemic. During the analysis severity and outcome of neurological manifestations range from simple headache to vague non-focal complaints to severe neurologic impairment associated with seizure or meningitis.

Conclusion & Relevance: Central and peripheral nervous system (CNS/PNS) manifestations were seen during the SARS-2002, MERS-2012 and COVID-19. However, none of the publication found with the primary or secondary objective of finding the neurological manifestation in the COVID-19 patients and their mechanism which strengthen the importance to start more precise clinical trials.

Key Points

Question: Is COVID-19 infection induce neurological manifestation and concern about the nervous system involvement during the course of infection?

Findings of Study

Systematic review was done in total 31 studies and 09 studies (n=11147) were included in the final meta-analysis. In our study, total of 09 studies (total 11147 patients) reported occurrence of CNS-PNS combined symptoms in COVID-19 positive patients, the proportion was 45.718%, 48.278% by random and fixed effect size model, respectively. As there was significant heterogeneity 95.53%, (95% CI for I^2 93.45 to 96.95), we used random effect model, whereas 9 studies (total 1114 patients) reported occurrence of CNS symptoms in COVID-19 positive patients, the proportion was 26.166%, 37.21% by random and fixed effect size model, respectively. As there was significant heterogeneity 95.19%, (95% CI for I^2 92.72 to 96.82), we used random effect model.

Meaning: Prevalence of combined CNS/PNS symptoms was found in about 46.8 to 48.311% of population which suggest that the concern of the neurological manifestations in COVID-19 patients. Therefore management require special attention to these patients.

Interpretation: The prevalence of neurological sign and symptoms were taken as primary objective. Thereafter, the prevalence of each CNS/PNS symptoms was categorized and their prevalence studied. The selection of Bagheri et al 2020 may be discussed because they have done the cross sectional study with the neurological finding and correlated the data with prevalence of the COVID-19 positive patients. The proportion of patients presenting with neurological outcome and clinical/PCR positivity were done, however we had searched and followed all the possible findings available on online/web source, therefore, the data collection process may remain a limitation of work. Due to lack of data of SARS-CoV and MERS-CoV we have included the case reports, MERS and COVID-19 in CNS/PNS manifestations.

Background

Severe acute respiratory syndrome namely corona-virus 2 (2019-nCoV) pandemic has changed the understanding and viewpoint of viral infection and given a cause to think more critically in the management of viral infection. SARS-CoV-2 is said to be the version 7.0 of corona virus family and of β -type. COVID-19 may be asymptomatic or have mild to severe pneumonia like syndrome.^{1,2} Several research recommended that 2019-nCoV is one of the predominant virus that specifically target the human respiratory system. SARS, MERS and COVID-19 essentially exhibit as respiratory distress, which represented through slight respiratory problem to a serious respiratory distress syndrome (ARDS) and incidentally adjunct to gastrointestinal appearances², cardiovascular and neurological conditions³. If we see the neurological capabilities is never been studies in any of the published literatures as a primary or secondary objectives. If we see the history of the corona virus family and its pandemic situations it came earlier in 2002 as SARS and MERS in 2012. But logically speaking the mortality rate worldwide indicate the prevailing high risk of the present 2019-nCoV compared to the other counterparts is more.⁵

The present systematic review and meta-analysis aimed to the evidence based its neurological manifestations and The common symptoms of nCoV-2019 infection start in 4-5 days with mild fever, mild to moderate cough, running nose and fatigue whereas other most common symptoms namely headache, hemoptysis, and dyspnea were reported in several studies. Moderate to severe cases of nCoV-2019 infection may worsen with the development of pneumonia, acute respiratory distress syndrome, acute cardiac problems, and multiorgan failure.⁵

Presently as on June 5, 2020 the complete Coronavirus Cases is 6,720,550, which precipitated 393,542 Deaths (5.85%) and nearly 3,264,238 recovered (48.57%)⁶. This suggests that COVID-19 pandemic is one of major world public health issue which World Health Organization (WHO) formally think about as a world pandemic on 11 March 2020 and named as, COVID-19 outbreak⁷. Studies suggesting about the nCoV-2019 infections may have related neurological manifestations (e.g., febrile seizures, convulsions, change in mental status, and encephalitis)^{8,9}. Very few reports have described the neurotropic and neuroinvasive abilities of corona viruses to humans, which suggest that nasal nCoV-2019 infection, get access to CNS thru the olfactory bulb inflammation and demyelination¹⁰. Therefore, in the current systematic review, we will talk about the proof on the incidence of CNS involvement and neurological manifestations in population with COVID-19.

Methods

Objectives

Incidence of the neurological manifestation in 2019-nCoV and prevailing prevalence in the context of previous CoV-SARS. Therefore y-the objective of the paper

1. Prevalence of neurological outcome in 2019-nCoV infected patients
2. Correlation of events in SARS, MERS and 2019-nCoV infection

3. Prevalence of CNS/PNS symptoms in all the corona pandemics
4. Network analysis of case reports of SARS, MERS and COVID-19

Search methods: The manuscript search is depending on the complete possible online sources. Out of total 1651 articles, finally we have included 32 articles for the systematic review and meta-analysis. The analysis were made in the two sections, one which is the current 2019-nCoV outbreak for the neurological/CNS manifestation and another is cumulative outcome of 2002 and 2012 SARS and MERS outbreak respectively.

Database search: Three independent reviewers AJ, HM and PS searched the Google Scholar, MEDLINE (Pubmed), EMBASE, OVID, Scopus, Science Direct and unpublished data were screened through Medrxiv and BioRxiv. The search strategy included both keyword and Medical Subject Headings (MeSH) terms. The keywords used were: "Neuro", "CNS", Central nervous System, "anxiety", "depression", "seizure", "agitation", "neurological", "2019-nCov", 2019 "novel corona virus", COVID-19, corona virus disease-2019, OR infarction for the corona virus -2 however, all previous studies for SARS-2002 and MERS-2012 where searched with the key words "corona virus- SARS" OR SARS OR SARS-CoV AND "corona virus-MERS OR MERS OR MERS-CoV". During the screening process we have kept no language restrictions and for articles written in languages other than English, google translate was used to obtain relevant information and extract data if possible, otherwise it was excluded from the analysis. In cases in which the translation cannot work out we have collected data only from the abstract (if it is in English). We retrieved the full text article of the potentially eligible study after screening the title, summary/ abstract and type of study as described by search result which met the eligibility criteria for current systematic review and meta-analysis. Databases were systematically searched thoroughly and duplicates were independently screened by authors (DP, NB, AB and HM). In the next phase articles were selected as per the titles/abstracts published and have the relevance as neurological outcome in COVID-19. For relevant articles, the full texts was obtained and evaluated as per neurological sign and symptoms in nCoV-19 infected patients. BM, MM, MG and AP were consulted for any discrepancy or confusion. Four authors (HS, DP, RS and NB) have extracted data independently by using pre-tested Cochrane data extraction form. After independently verifying by BM, MM, MG and AP, the data was entered into *MedCalc* software and analyzed.

Selection criteria: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) were followed to analyze and report systematic review and meta-analysis (Figure. 1). The registration of the review protocol was not previously done. The thorough search engine were used to collect all possible studies through Google scholar, MEDLINE (Pub Med), EMBASE, OVID, Cochrane Central Library, CNKI, Medrxiv and BioRxiv and Scopus till May 15, 2020.

Statistical analysis: To analyze the differences in neurological impact, levels of anosmia/hyposmia, dyspnea, headache, headache and loss of consciousness were calculated according to the number of respondents per response to the number of total patients as categorical variables. Differences categorical variables were analyzed for proportion analysis by chi-squared test. We used network analysis to correlate with the different pandemics namely SARS-2002, MERS-2012 and COVID-19. Data were analyzed by using the "MedCalc Statistical Software version 19.2.6 (MedCalc Software bv, Ostend, Belgium; <https://www.medcalc.org>; 2020)" and reported as pooled prevalence using a fixed and random effect model. Heterogeneity was investigated (standard χ^2 test) and represented as I^2 for the degree of inconsistency. Analyzed report showed both fixed effect and random effect model as necessary as an indication of the variability in the studies. The significant level set at $p < 0.05$ and prevalence range were represented as 95% CI. Publication bias in the selected study was evaluated by plotting the funnel plot and done the analysis accordingly.

Results

Inclusion/exclusion of studies: Total 2615 articles were found in databases search and after duplicate, title and summary screening articles reduced to 1651, thereafter, a total of 1459 articles were excluded. Full-text screening of the remaining 1156 articles was done. Among these studies, after full-text screening, a total of 31 articles were included in the final review. (Figure 1)

Data collection and analysis: A total of 1651 articles were found after preliminary screening of the databases. After title and abstract screening, a total of 495 articles were excluded. Full-text screening of the remaining 1156 articles was done. Among these studies, after full-text screening, a total of 247 articles were included in the final review. The PRISMA flowchart of the study is shown in Figure 1, 215 articles were excluded after full-text screen (Not related to neurological manifestation=32, Reports (incomplete data)= 78, *In silico / in vitro* study= 30, Management of SARS, MERS or COVID-19= 55, Incomplete epidemiological study= 20). Details of studies with neurological manifestation in SARS-2002, MERS-2012 and COVID-19 summarized in Table 1,2 & 3.

Prevalence of nervous system complication/manifestations in COVID-19 positive patients

Overall prevalence of central and peripheral nervous system (CNS/PNS) symptoms

A total of 09 studies (total 11147 patients) reported occurrence of CNS-PNS combined symptoms in COVID-19 positive patients, the proportion was 48.278 %, 45.718% by fixed and random effect size model, respectively. As there was significant heterogeneity 96.00%, (95% CI for I^2 94.08 to 97.29), we used random effect model. The forest plot is showed in Figure 2a. No significant publication bias was seen (Figure 2b).

Overall prevalence of nervous system symptoms (CNS)

A total of 08 studies (total 1078 patients) reported occurrence of CNS symptoms in COVID-19 positive patients, the proportion was 25.184 % & 34.890 % by fixed and random effect size model, respectively. As there was significant heterogeneity 95.32 %, (95% CI for I^2 92.75 to 96.98)($P < 0.0001$), we used random effect model. The forest plot is showed in Figure 3a. Publication bias was seen, may be due to less number of publication. (Figure 3b).

Overall prevalence of peripheral nervous system (PNS) symptoms

A total of 08 studies (total 11009 patients) reported occurrence of PNS symptoms in COVID-19 positive patients, the proportion 41.366 % & 48.386 % by random and fixed effect size model, respectively. As there was significant heterogeneity 98.82 % (95% CI for I^2 98.43 to 99.11) ($P < 0.0001$), we used random effect model. The forest plot is showed in Figure 4a. No significant publication bias was seen (Figure 4b).

Prevalence of ANSOMIA/HYPOSMIA as symptoms

A total of 3 studies (total 10769 patients) reported occurrence of ANSOMIA/HYPOSMIA symptoms in COVID-19 positive patients, the proportion 48.547%, 37.270% by random and fixed effect size model, respectively. As there was significant heterogeneity 99.47% (95% CI for I^2 99.26 to 99.61), we used random effect model. The forest plot is showed in Figure 5a. Publication bias was seen, may be due to very less number of publication. (Figure 5b).

Overall prevalence of nervous system symptoms (Myalgia)

A total of 2 studies (total 77 patients) reported occurrence of Myalgia symptoms in COVID-19 positive patients, the proportion 21.279%, 19.994% by random and fixed effect size model, respectively. As there was significant heterogeneity 95.40% (95% CI for I^2 86.48 to 98.44), we used random effect model. The forest plot is showed in Figure 6a. No significant publication bias was seen (Figure 6b).

Overall prevalence of nervous system symptoms (Fatigue)

A total of 2 studies (total 135 patients) reported occurrence of Fatigue symptoms in COVID-19 positive patients, the proportion 24.674% & 30.810% by fixed and random effect size model, respectively. As there was significant heterogeneity 91.33% (95% CI for I^2 69.43 to 97.54) ($P = 0.0007$), we used random effect model. The forest plot is showed in Figure 7a. No significant publication bias was seen (Figure 7b).

Overall prevalence of nervous system symptoms (Dyspnea)

A total of 5 studies (total 731 patients) reported occurrence of Dyspnea symptoms in COVID-19 positive patients, the proportion 15.419 % & 26.131% by fixed and random effect size model, respectively. As there was significant heterogeneity 95.48 % (95% CI for I^2 92.01 to 97.44) ($P < 0.0001$), we used random effect model. The forest plot is showed in Figure 8a. No significant publication bias was seen (Figure 8b).

Overall prevalence of nervous system symptoms (Headache)

A total of 3 studies (total 629 patients) reported occurrence of Headache symptoms in COVID-19 positive patients, the proportion 10.263%, 9.727% by random and fixed effect size model, respectively. As there was not significant heterogeneity 52.06% (95% CI for I^2 0.00 to 86.21), we used random effect model. The forest plot is showed in Figure 9a. No significant publication bias was seen (Figure 9b).

Overall prevalence of nervous system symptoms (Impaired Consciousness)

A total of 2 studies (total 629 patients) reported occurrence of Impaired Consciousness symptoms in COVID-19 positive patients, the proportion 9.471%, 13.580% by random and fixed effect size model, respectively. As there was significant heterogeneity 83.49% (95% CI for I^2 31.48 to 96.02), we used random and fixed effect model. The forest plot is showed in Figure 10a. No significant publication bias was seen (Figure 10b).

Network analysis of neurological manifestations

The network analysis of case reports ($n=103$) showed the neuronal manifestation of COVID-19 and other CoV infection is widely correlated with each other, whereas, analysis showed that the COVID-19 pandemic have more degree of neuronal manifestation as compared with other SARS and MERS pandemics in 2002 and 2012 respectively. (Figure 11) The number of study reported in previous SARS-CoV and MERS-CoV infection were minimal as compared to the COVID-19 reporting. The individual neuronal manifestation of CNS or PNS nature ranges from simple headache to the Seizure or GBS and even Lau KK et al, 2004³³ reported Myalgia and Al-Hameed FM et al, 2017 reported of GTC (Seizure)³⁸ by Intracerebral hemorrhage. Kim JE et al, 2017³⁹ reported Guillain–Barré syndrome (GBS), confusion and seizure of several patients. However, in the recent nCoV-2019 pandemic it was seen more neurological involvement i.e. Duong L et al, 2020¹⁹ and Moriguchi T, et al, 2020²² have reported about the meningoencephalitis, Scheidl et al, 2020²⁴, Sedaghat Z et al, 2020²⁵, Toscano G, et al 2020²⁷, Virani A et al, 2020²⁸ and Zhao H et al, 2020²⁹ have reported of Guillain–Barré syndrome. (Table 2 & 3; Figure 12)

Gutiérrez-Ortiz C et al, 2020⁴⁶ reported the single event of Miller Fisher Syndrome and polyneuritis cranialis as neurological manifestations, proposed the absence of immune response during COVID-19.

Discussion

The present systematic review and meta-analysis revealed that the pattern of neurological manifestation of nCoV-2019 is related to the previous two pandemics i.e. SARS-2002 and MERS-2012. The main clinical manifestations of SARS and MERS were fever, chills, dry cough, and difficulty breathing which is related to the 2019-nCoV symptoms as well. In moderate to severe cases, respiratory failure associated with multiple organ involvement may occur³³. In addition, these patients found to be neurological manifestations such as encephalitis, polyneuropathy, and aortic ischemic stroke³⁸. An autopsy sample revealed overall deteriorating findings namely infiltration of monocytes and lymphocytes in the vessel wall, ischemic changes of neurons, demyelization of nerve fibers to the cerebral edema and meningeal vasodilation in patients.

Present systematic review and metaanalysis aimed to access the neurological manifestation of nCoV-2019 infection were further classified as central nervous system (CNS) symptoms namely dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and epilepsy and peripheral nervous system (PNS) symptoms like hypoplasia, hyposmia, neuralgia, and hypogeusia were studied¹⁶.

In Study by Hung EC et al, 2003³¹ showed SARS positive evidenced in CSF sample of SARS-CoV and genome sequences of SARS in brain sample (Gueta et al., 2005; Zhanget al., 2003). MERS outbreak in 2012-13 also reported delirium, neuropathy and acute cerebrovascular disease^{35, 37} where as Saad et al, 2014²¹ reported confusion and seizures in 18 and 6 of the participants, respectively out of 70 MERS patients. Therefore, published literature showed the indication of neurotropism by the CoV- family. Recent study by Moriguchi, et al. 2020²², showed patients with SARS-CoV-2 suffered from meningitis / encephalitis which were confirmed by RT-PCR detection in cerebrospinal fluid. The exact reason is unclear, but the few described in the literature are, development of focal meningitis/encephalitis affecting the rhino- or gustatory-cortex representations or appropriate sub-cortical ascending/descending tracts in the CoV positive patients is one of the reason which may be easily detect viral-RNA in the cerebrospinal fluid (CSF) of infected patients^{16, 22}. In our network study meningitis/encephalitis, seizure and confusion were well connected to the MERS and COVID-19.

The symptoms of PNS appeared due to involvement of peripheral nerves, including the cranial nerves which further associate to cranial nerves I, VII, IX, and X by SARS-CoV 2⁴⁷. Our study reported common neurological sign and symptoms were dyspnea (15.419 % & 26.131 %), fatigue, myalgia (19.994%-21.279) , loss of consciousness (9.471% to 13.580%) and agnosia. However, few case reports have reported even more severe neurological manifestation like seizure, GBS or meningitis/encephalopathy. (Figure 11, 12) However, none of the studies observed the viral neurotropism but few author have reported that the patients with neurological manifestation have the positive CSF of COVID-19³⁹. Therefore, it is very early to explain the event whether neurological dysfunction is due to direct viral injury or systemic disease.

The other school of thought showed that the neurotropism of CoV family occur mainly through two pathways, i.e. the hematogenous and neuronal retrograde courses of CNS infection through respiratory infection. An animal study showed MERS-CoV tissue pantropism occur after the viral entry into blood stream through endothelial infection in the choroid plexus^{23, 40}.

High mortality and fast spread of the CoV-family namely SARS, MERS and 2019-nCoV infection due to the high fusion of these virus and rapid replication involved angiotensin-converting enzyme 2 (ACE2) receptor which is present throughout the vital organs¹⁷. Therefore, the presence of ACE 2 receptor in brain is an important factor and link to study the neurological manifestation and management in 2019-nCoV infection. Patel AB, 2020⁴¹ described that there is evidence for a major involvement of excessive brain ACE/ Ang II/ AT-1R axis in increased activation of oxidative stress, apoptosis and neuroinflammation causing neurodegeneration and other brain disorders. At last the probable chance of neurological manifestation may be due to the cytokines overload and reduced immunity. Immunoinflammation plays an

important role in viral infection and which leads to the systemic inflammatory response syndrome (SIRS)⁴². *In vitro* study suggested that primary glial cells released a large number of inflammatory cytokines namely IL-6, IL-12, IL-15, and TNF- α after being infected with CoV⁴³. Further, study suggests that virus-induced SIRS or SIRS-like immune disorders may cause mortality due to involvement of macrophages, microglia, and astrocytes in the CNS⁴⁴.

Abbreviations

SARS: Severe Acute Respiratory Syndrome; MERS: Middle East respiratory syndrome; ARDS: Serious respiratory distress syndrome; COVID-19: Coronavirus Disease 19; nCoV-2019: Corona virus 2019; SIRS: Systemic inflammatory response syndrome; RT-PCR: Real time polymerase chain reaction

Declarations

Authors Contributions

After the conception of idea of study AP and BM have designed the study with DP, MM and MG. Systematic databases were searched thoroughly by authors HM, DP, PS, NB, PS and AB. Articles were selected as per the titles/abstracts published and have the relevance as neurological outcome in COVID-19. For relevant articles, the full texts was obtained and evaluated as per neurological sign and symptoms in nCoV-19 infected patients. BM, MM, MG and AP were consulted for any discrepancy. Four authors (HS, DP, RS and NB) were extracted the data independently by using pre-tested Cochrane data extraction form. After independently verifying by BM, MM, MG and AP, the data was entered into MedCalc software for review and interpretation.

Declarations of interest: The authors have declared that there is no conflict of interest.

Disclaimer: All statements in this systematic review, including its findings and conclusions, are solely those of the author's analysis and viewpoints.

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Tables

Table: 1; Published observational/cross sectional studies which reported the neurological manifestation to the COVID-19 positive patients

Author, year	Sample Size (SS)	Type of Study (ST)	Patient Population	Treatment	Neurological condition (NC)	2019-nCoV Presence and diagnosis	Type of NS involvement (CNS/PNS) (NSI)	Remarks
Bagheri et al 2020 ¹⁰	10069	Cross-sectional study	COVID-19	NA	Anosmia/Hyposmia (48.23%)	NA	PNS	Olfactory dysfunction happened in Iran during the COVID-19 epidemic, that correlates with the number of patients infected with COVID-19 across the country.
Chen N <i>et al</i> , 2020 ¹¹	99	Observational	COVID-19 positive	Oseltamivir, Ganciclovir, Lopinavir Ritonavir, Cephalosporins, Quinolones, Carbapenems, tigecycline	Dyspnea (21 [58.33%] patients), Fatigue (17 [47.22%] patient).	RT-PCR	CNS & PNS	2019-nCoV was of clustering onset, is more likely to infect older men with co-morbidities.
Helms J, 2020 ¹²	64	Observational	COVID-19 positive	Midazolam Propofol Sufentanil	Neurological sign (49/58) Agitation (40/58) Confusion (26/58), enhanced tendon reflexes, ankle clonus, and bilateral extensor plantar reflexes (39/58), inattention, disorientation, or poorly organized movements (15/45) Cerebral ischemic stroke (3/13) Encephalopathy (1/8)	RT-PCR CSF	CNS & PNS	At the initial stage author have unable to decide the features of critical illness-related encephalopathy, cytokines, or the effect or withdrawal of medication, and which features were specific to SARS-CoV-2 infection.
Huang C <i>et al</i> , 2020 ¹³	41		COVID-19 positive	Remdesivir Lopinavir and Ritonavir Corticosteroid	Headache (3/38), Dyspnea (22/40), Myalgia (18/41)	RT-PCR	CNS & PNS	The neurological sign and symptoms appear in around 3% to 44% of patients.
Huang Y <i>et al</i> , 2020 ¹⁴	36	Observational	COVID-19 positive	Oseltamivir, Ganciclovir, Ribavirin Orumifenovir hydrochloride(35/36)	Shortness of breath (21/36), Dyspnea (14/36) Disturbance of consciousness (8/36), Fatigue (17/36) Myalgia (1/36)	RT-PCR	CNS & PNS	Reported most non-survivors are older men with comorbidities conditions especially cardiovascular diseases and COPD.
Lechien JR <i>et al</i> , 2020 ¹⁵	417	Observational	COVID-19 positive	NA	Anosmic (284/417) Hyposmic (73/417) Dyspnea (54/417)	Nasopharyngeal swab test (RT-PCR)	CNS	Suggested to report anosmia or ageusia as important symptoms of the COVID-19 infection.
Mao L <i>et al</i> , 2020 ¹⁶	214	Observational	COVID-19 positive	NA	Neurological sign (78/214) Headache (28/214), Dizziness (36/ 214), Impaired consciousness(16/78), ataxia, acute cerebrovascular disease (6/78) and Epilepsy Peripheral nervous system (PNS) symptoms skeletal muscular symptoms (23/78) Hypogeusia (12/214) Hyposmia (11/214)	Head CT, Swab test	CNS & PNS	Non-severe severe COVID-19 patients reported neurologic symptoms manifested as acute cerebrovascular diseases, consciousness impairment and skeletal muscle symptoms.
Wang D <i>et</i>	138	Observational	COVID-19	Oseltamivir	Headache (9),	RT-PCR	CNS	Identified common sign

<i>al,2020</i> ¹⁷			positive	Methylprednisolone Azithromycin Moxifloxacin, Ceftriaxone,	Dizziness (13), Dyspnea (5)			and symptoms at COVID-19 onset were fever, dry cough, myalgia, fatigue, dyspnea, and anorexia.
Wang Z et al, 2020 ¹⁸	69	Observational	COVID-19 positive	oxygen support, Corticosteroids, Moxifloxacin	Dyspnea (15/69), Dysgeusia (5/69), Ageusia (1/69), Hyposmia (3/69), Dysgeusia and hyposmia (2/69), Dysgeusia and anosmia (2/69), Ageusia and hyposmia (2/69), Ageusia and anosmia (5/69)	nasopharyngeal swab test (RT- PCR	CNS & PNS	Older patients or those with underlying comorbidities are at higher risk of death.

Table: 2; Published case reports of neurological manifestations in COVID-19 positive patients

Author, year	Sample Size (SS)	Type of Study (ST)	Patient Population	Treatment	Neurological condition (NC)	2019-nCoV Presence and diagnosis	Type of NS involvement (CNS/PNS) (NSI)	Remarks
Duong L et al, 2020 ¹⁹	01	case report	COVID-19	(Ceftriaxone and Vancomycin, Acyclovir, HCQ	Meningoencephalitis	PCR (CSF- NA)	CNS	They have observed a COVID-19 infection presenting as an isolated meningoencephalitis without respiratory involvement.
Karimi N et al, 2020 ⁰⁸	01	Case report	COVID-19 positive	chloroquine and Lopinavir-ritonavir	GTC convulsion	Brain MRI	CNS	Association between frequent seizures and COVID-19 may be due to encephalitis and the invasion of the virus to the brain or toxic effect of inflammatory cytokines.
Moriguchi T, et al, 2020 ²²	01	Case Report		Laninamivir and antipyretic	Meningitis/encephalitis		CNS	specific SARS-CoV-2 RNA was not detected in the nasopharyngeal swab, it was detected in CSF
Paniz-Mondolfi A et al, 2020 ²³	01	Case report	COVID-19 positive	HCQ & Enoxaparin	Confusion Agitation and combative.	nasopharyngeal swab test (RT-PCR positive)	CNS	Transmission electron microscopy of sections obtained at post-mortem examination revealed the presence of 80 to 110 nm viral particles in frontal lobe brain sections
Scheidl et al, 2020 ²⁴	01	Case report	COVID-19 positive	NA	Guillain Barre syndrome	RT-PCR positive	PNS	Our case draws attention to the occurrence of GBS also in patients with COVID-19 (corona virus disease 2019), who did not experience respiratory or general symptoms.
Sedaghat Z et al, 2020 ²⁵	01	Case report	COVID-19 positive	HCQ, Lopinavir/ Ritonavir (LPV/RTV) Azithromycin.	Guillain Barre syndrome	RT-PCR positive	PNS	Suggested the treatment with IVIG or plasmapheresis should be initiated along with antiviral treatment.
Somani S et al, 2020 ²⁶	01	Case report		levetiracetam, lacosamide, Phenytoin, Midazolam	Dyspnea (1/2) Myalgias (1/2) Myoclonic status Epilepticus with coma (MSE) (1/2)	RT-PCR positive	CNS & PNS	Asymptomatic COVID-19. Altered mental status in patients with COVID-19

Toscano G, et al 2020 ²⁷	05	Correspondence	COVID-19 positive (4/5)	Intravenousimmunoglobulin(IVIG)	Guillain-Barré syndrome	RT-PCR positive	PNS	First symptoms of Guillain-Barré syndrome is similar to the interval seen with Guillain-Barré syndrome that occurs during or after other infections
Virani A et al, 2020 ²⁸	01	Case report	COVID-19 positive	Intravenousimmunoglobulin(IVIG) HCQ	Guillain-Barré syndrome	RT-PCR positive	PNS	Author cognizant of the neurological presentation of GBS that is likely associated with SARS-CoV-2 infection.
Zhao H et al, 2020 ²⁹	01	Case Report	COVID-19 positive	Arbidol, Lopinavir, Ritonavir	Guillain-Barré syndrome.	RT-PCR positive	PNS	Study showed a possible causal association between Guillain-Barré syndrome and SARS-CoV-2 infection

NS: Nervous system; HCQ: Hydroxy chloroquine;

Severe Acute Respiratory Syndrome (SARS-CoV)

Sample Size	Type of Study	Patient Population	Treatment	Neurological condition	2019-nCoV Presence and diagnosis	Type of NS involvement (CNS/PNS) (NSI)	Remarks
01	Case Report	SARS-CoV	Broadspectrum antibiotics and inhalation of Ribavirin	Myalgia (Weakness and numbness in both legs)	chest x-ray (CXR), PCR	PNS	Systemic inflammatory response syndrome, has been proposed to play a role in the nerve damage.
01	Case Report	SARS-CoV	Ribavirin Propofol Phenytoin	Seizure	RT-PCR, CSF	CNS	First reported the entry of SARS-CoV into the CSF.
01	Case Report	SARS-CoV	Ribavirin, Prednisolone	Anosmia	RT-PCR	PNS	Anosmia persisted during more than two years of follow-up.
01	Case Report	SARS-CoV	Ribavirin hydrocortisone	Myalgia GTC	RT-PCR CSF-P	CNS & PNS	Generalized convulsion with a positive RT-PCR for SARS-CoV in the CSF suggests possible infection of the central nervous system by SARS-CoV.
05	Observational	SARS-CoV	Immunoglobulin (IVIg), Methylprednisolone, Ribavirin, Convalescent serum, LMWH	Loss of consciousness (1/5) Infarction (5/5)		CNS	Out of 206, 05 patients experience neurological manifestations. All five have experience d cerebral infarction.

Middle East respiratory syndrome corona virus (MERS-CoV)

Sample Size	Type of Study	Patient Population	Treatment	Neurological condition	2019-nCoV Presence and diagnosis	Type of NS involvement (CNS/PNS) (NSI)	Remarks
02	Observational	MERS-CoV positive	Intravenous hydration, Tazocin, Azithromycin	Headache, Nausea, and vomiting. Myalgia, Dizziness Intracerebral hemorrhage	RT-PCR	CNS & PNS	CT showed right frontal lobe intracerebral hemorrhage with massive brain edema and midline shift of 02 patients among 120 patinets.
03	Observational	MERS-CoV positive	NA	Ataxia (1/3), Vomiting (2/3), Confusion(2/3) Dysmetria (1/3) Dyspnea and hypoxia (1/3) Encephalitis (1/3)	RT-PCR and CSF	CNS & PNS	Brain MRI revealed striking changes characterized by widespread, bilateral hyperintense lesions on T2-weighted imaging within the white matter and subcortical areas of the frontal, temporal, and parietal lobes, the basal ganglia, and corpus callosum.
01	Case report	MERS-CoV	Peginterferon Alpha-2a, Ribavirin,	Intracerebral hemorrhage	RT-PCR	CNS	Neurological symptoms associated with MERS-COV

		positive	and Methylprednisolone (i.v.)	Shortness of breath			
04/23	Observational	MERS-CoV positive	Interferon alpha-2a, Ribavirin, and Lopinavir/ Ritonavir	Dyspnea (2/4) Myalgia or arthralgia (2/4) Guillain-Barré syndrome (2/4) Acute sensory neuropathy (3/4) Headache (2/23) Confusion (5/23) Seizure (0/23) Nausea and vomiting (18/23)	RT-PCR	CNS & PNS	GBS, ICU-acquired weakness, or acute sensory neuropathy that resulted from a toxin or infection
70	Observational	MERS-CoV positive	NA	Shortness of breath (42/70) Fatigue (29/70) Myalgia or arthralgia (14/70) Vomitting (21/70) Headache (9/70) Confusion (18/70)	RT-PCR		MERS-CoV can cause severe infection in the age ≥65 years with more requirement of intensive care and a high mortality.

NA: Not Available; RT-PCR: Real-time Polymerase chain Reaction; CSF: Cerebrospinal fluid; GTC: Generalized tonic clonic seizure; i.v.: Intravenous; CT: computed tomography

Figures

Figure 1

PRISMA chart showing study section criteria and process

Figure 2

a: Forest plot showing pooled prevalence of CNS-PNS combined among patients with COVID-19 patients. b: Funnel plot showing publication bias among studies evaluating neurological complications of COVID-19.

Figure 3

a: Forest plot showing pooled prevalence of CNS complication among patients with COVID-19. b: Funnel plot showing publication bias among studies evaluating neurological complications of COVID-19.

Figure 4

a: Forest plot showing pooled prevalence of PNS complications among patients with COVID-19. b: Funnel plot showing publication bias among studies evaluating neurological complications of COVID-19.

Figure 5

a: Forest plot showing pooled prevalence of ANSOMIA/HYPOSMIA complications among patients with COVID-19. b: Funnel plot showing publication bias among studies evaluating neurological complications of COVID-19.

Figure 6

a: Forest plot showing pooled prevalence of Myalgia among patients with COVID-19. Incidence of Myalgia symptoms. b: Funnel plot showing publication bias among studies evaluating neurological complications of COVID-19.

Figure 7

a: Forest plot showing pooled prevalence of Fatigue among patients with COVID-19. b: Funnel plot showing publication bias among studies evaluating neurological complications of COVID-19.

Figure 8

a: Forest plot showing pooled prevalence of Dyspnea among patients with COVID-19. b: Funnel plot showing publication bias among studies evaluating neurological complications of COVID-19.

Figure 9

a: Forest plot showing pooled prevalence of Headache among patients with COVID-19. b: Funnel plot showing publication bias among studies evaluating neurological complications of COVID-19.

Figure 10

a: Forest plot showing pooled prevalence/incidence of Impaired Consciousness among patients with COVID-19. b: Funnel plot showing publication bias among studies evaluating neurological complications of COVID-19.

Figure 11

Overall Network analysis which showed the relationship with three main pandemics i.e. SARS-2002, MERS-2012 and COVID-19 with the CNS, PNS or combined manifestations. Note: The size of node define the degree of relation with the

individual neurological symptoms and increased number of edge give the increased relation with the respective nodes. (Edges showing directed association, Node size depicts degree of nodes)

Figure 12

Network analysis showed the impact of neurological manifestation as per described symptoms in case report as well as observational studies. Note: The size of node define the degree of relation with the individual neurological symptoms and increased number of edge give the increased relation with the respective nodes. (Edges showing directed association, Node size depicts degree of nodes)