Saber Soltani, Alireza Tabibzadeh, Armin Zakeri, Amir Mohammad Zakeri, Tayebeh Latifi, Mahdi Shabani, Amir Pouremamali, Yousef Erfani, Iraj Pakzad, Pooneh Malekifar, Reza Valizadeh, Milad Zandi* and Reza Pakzad*

COVID-19 associated central nervous system manifestations, mental and neurological symptoms: a systematic review and meta-analysis

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Abstract: The ongoing pandemic of Coronavirus disease 2019 (COVID-19) has infected more than 27 million confirmed cases and 8,90,000 deaths all around the world. Verity of viral infections can infect the nervous system; these viral infections can present a wide range of manifestation. The aim of the current study was to systematically review the COVID-19 associated central nervous system manifestations, mental and neurological symptoms. For that we conducted a comprehensive systematic literature review of four online databases, including Web of Science, PubMed, Scopus and Embase. All relevant articles that reported psychiatric/psychological symptoms or disorders in COVID-19 without considering time and language restrictions were assessed. All the study procedures were performed based on the PRISMA criteria. Due to the screening, 14 studies were included. The current study result indicated that, the pooled prevalence of CNS or mental associated disorders with 95% CI was 50.68% (6.68–93.88). The most prevalence symptoms were hyposmia/anosmia/olfactory dysfunction (number of study: 10) with 36.20% (14.99–60.51). Only one study reported numbness/paresthesia and dysphonia. Pooled prevalence of numbness/paresthesia and dysphonia was 5.83% (2.17–12.25) and 2.39% (10.75–14.22). The pooled prevalence of depression and anxiety was 3.52% (2.62–4.54) and 13.92% (9.44–19.08). Our findings demonstrate that COVID-19 has a certain relation with neurological symptoms. The hypsomia, anosmia or olfactory dysfunction was most frequent symptom. Other symptoms were headache or dizziness, dysgeusia or ageusia, dysphonia and fatigue. Depression, anxiety, and confusion were less frequent symptoms.

Keywords: central nervous system; COVID-19; neurological symptoms; psychiatric symptoms; SARS-CoV-2.

Saber Soltani and Alireza Tabibzadeh contributed equally to this article.

***Corresponding authors: Milad Zandi**, Department of Virology, School of Public Health, Tehran University of Medical Sciences, 1417613151, Tehran, Iran; and Students' Scientific Research Center, Tehran University of Medical Sciences, 1417613151, Tehran, Iran, E-mail: miladzandi416@gmail.com. https://orcid.org/0000-0002-2145-0196; and **Reza Pakzad**, Department of Epidemiology, Faculty of Health, Ilam University Medical Sciences, 6939177143, Ilam, Iran; and Noor Research Center for Ophthalmic Epidemiology, Noor Eye Hospital, 1417613151, Tehran, Iran, E-mail: rezapakzad2010@yahoo.com. https://orcid.org/0000-0001-8133-3664

Saber Soltani, Department of Virology, School of Public Health, Tehran University of Medical Sciences, 1417613151, Tehran, Iran; and Research Center for Clinical Virology, Tehran University of Medical Sciences, 1417613151, Tehran, Iran, E-mail: sabersoltani71@gmail.com

Alireza Tabibzadeh, Department of Virology, Iran University of Medical Sciences, 1449614535, Tehran, Iran, E-mail: alireza.tabibzadeh@outlook.com

Armin Zakeri, Department of Hematology, Faculty of Medical Sciences, Tarbiat Modares University, 111-14115, Tehran, Iran, E-mail: zakeri.armin24@yahoo.com

Amir Mohammad Zakeri, Pediatric Surgery Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, 22439962,Tehran, Iran, E-mail: amirm.zack@gmail.com

Tayebeh Latifi and Mahdi Shabani, Department of Virology, School of Public Health, Tehran University of Medical Sciences, 1417613151, Tehran, Iran, E-mail: T.latifi1992@gmail.com (T. Latifi), mehdi_shabani1371@yahoo.com (M. Shabani)

Amir Pouremamali, Department of Medical Virology, Faculty of Medical Sciences, Tarbiat Modares University, 111-14115, Tehran, Iran, E-mail: a.pouremamali@modares.ac.ir

Yousef Erfani, Department of Medical Laboratory Sciences, School of Allied Medical Sciences, Tehran University Medical Sciences, 1417613151, Tehran, Iran, E-mail: yerfani@tums.ac.ir

Iraj Pakzad, Department of Microbiology, School of Allied Medical Sciences, Ilam University Medical Sciences, 6939177143, Ilam, Iran, E-mail: pakzadi2006@gmail.com

Pooneh Malekifar, Department of Epidemiology, School of Public Health, Tehran University Medical Sciences, 1417613151, Tehran, Iran, E-mail: poonehmalekifar@gmail.com

Reza Valizadeh, Department of Psychiatry, Psychosocial Injures Research Center, Ilam University Medical Sciences, 6939177143, Ilam, Iran, E-mail: Dr.reza.valizade@gmail.com

Introduction

The ongoing pandemic of Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2 (severe acute respiratory syndrome-coronavirus-2) (Soltani 2020), has infected more than 27 million confirmed cases and 8,90,000 deaths all around the world (World Health Organization 2020). The COVID-19 mean incubation period consider as 2–5 days (Wiersinga et al. 2020). The COVID-19 associated symptoms and death timeline ranged from 6 to 41 days, with a median of 14 days (Wang et al. 2020). The age and the patient's immune system are critical factors in COVID-19 outcome (Wang et al. 2020). The most common presented symptoms in COVID-19 patients are fever, cough and fatigue; whereas other symptoms include sputum production, headache, hemoptysis, diarrhea, dyspnea, and lymphopenia were reported (Carlos et al. 2020; Huang et al. 2020; Ren et al. 2020).

Verity of viral infections can infect the nervous system; these viral infections can present a wide range of manifestation including severe encephalitis, toxic encephalopathy and severe acute demyelinating lesions developing after viral infections (Michalicova et al. 2017; Wright et al. 2008). Some viruses are neurotropic or infect immune cells of central nervous system (CNS) microglia or astrocytes (Al-Obaidi et al. 2018; Soung and Klein 2018). SARS-CoV-2 is highly homologous with SARS-CoV (Grifoni et al. 2020). Recent emergent coronaviruses, SARS-CoV and MERS-CoV can infect CNS in patients and animal models (Li et al. 2020). The possibility of SARS-CoV-2 infection in the CNS and conducting neurological damage is not negligible. Also, both SARS-CoV-2 and SARS-CoV invades human cells by angiotensin-converting enzyme-2 (ACE-2) (Hoffmann et al. 2020), an essential component of the renin-angiotensin system in the brain (Abiodun and Ola 2020). Neurological symptoms were reported in COVID-19 patients. These manifestations could be presented as headache, disturbed consciousness and paresthesia. A study of 214 COVID-19 patients introduced that the incidence of neurological damage caused by SARS-CoV-2 estimated as 36.4% (Mao et al. 2020). Previous studies in the field of the COVID-19 neurological manifestations are focused on the case reports of neurological manifestations (Ellul et al. 2020; Tsivgoulis et al. 2020). The aim of the current study was to comprehensively update previous studies in the field of the COVID-19 neurological manifestations. Also, due to the ongoing COVID-19 pandemic, the aim of the current review and meta-analysis was to systematically review the COVID-19 associated central nervous system manifestations and neurological symptoms.

Methods

Search strategy and screening

All the study procedures were conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al. 2009). We conducted a comprehensive systematic literature review of four online databases, including Web of Science, PubMed, Scopus and Embase. All relevant articles that reported psychiatry/psychology symptoms/disorders in COVID-19 without considering time and language restrictions were retrieved. Social Science Research Network and MedRxiv searched to obtain unpublished or preprints. Google scholar was used for grey literature access. Search was conducted by using following keywords, "COVID-19", "Coronavirus", "Neurologic", "Central nervous system", "SARS-CoV-2", "Psychiatry", and "Psychology". The PICO in this study was as follows:

Population: child and adult with Covid-19

Intervention: none

Comparison: none

Outcome: Psychiatry/Psychology disorders/syndromes/signs/symptoms

The details of the search strategy are presented in Table 1.

The conducted search result imported in EndNote Version. X9 (Thomson Reuters) and after duplicate removal the screening was performed. The screening in three steps was performed by title and abstract and full text. All included studies met the inclusion criteria. The screening was performed by two independent authors (RP & SS) and the third expert author (IP) strategy was used for conflicts. Blinding and task separation were applied in the study selection procedure. The inter-rater agreement was 92%. All of the studies on the field of the COVID-19 associated central nervous system manifestations and neurological symptoms were included. The exclusion criteria for current study were case report and case series studies conducted in less than five patients as sample size.

Table 1: Search strategy based on PICO for MEDLINE.

1. COVID-19 [text word] OR COVID-19 [Mesh term]
2. Coronavirus [text word] OR Coronavirus [Mesh term]
3. SARS-CoV-2 infection [text word] OR SARS-CoV-2 infection [Mesh term]
4. 1 OR 2 OR 3
5. Syndromes [text word] OR Syndromes [Mesh term]
6. Disorders [text word] OR Disorders [Mesh term]
7. characteristic [text word] OR characteristic [Mesh term]
8. Symptoms [text word] OR Symptoms [Mesh term]
9. Sign [text word] OR Sign [Mesh term]
10. 5 OR 6 OR 7 OR 8 OR 9
11. Psychiatry [text word] OR Psychiatry [Mesh term]
12. Psychology [text word] OR Psychology [Mesh term]
13. 11 OR 12
14. 4 AND 10 AND 13

MeSH, Medical Subject Headings.

Data extraction

In the current study, any psychiatric disorders/psychology in COVID-19 patient were reviewed in addition other information's such as name of the author, the publication year, the country, study design, sample size and participants age was extracted. Also other general symptoms include mental disorder, confusion, depression, dementia, anxiety, fatigue/weakness, sleep disorder/drowsiness, delirium, cerebrovascular disease, nervous system disorders, headache, dizziness, dysphonia, hyposmia/anosmia/olfactory dysfunction, dysgeusia/ageusia, auditory dysfunction and numbness/paresthesia were extracted.

Quality assessment

The Newcastle-Ottawa Scale (NOS) scale (Wells et al. 1999) was used for assessing the quality of included studies. The scaling of included studies was performed as previous research (Hashemi et al. 2020). This scale has three sections: 1-selection (4 items, maximum score: 4 points), 2-Confounder (1 item, maximum score: 1 points), and 3-Exposure (2 items, maximum score: 2 points). The studies were evaluated by two raters (RP & SS) independently, and a total score was calculated for each study. The studies were then assigned to one of the following categories accordingly: very good studies: 6–7 scores; good studies: 4–5 scores; satisfactory studies: 2–3 scores; unsatisfactory studies: 0–1 score.

Statistical analysis

The Stata version 14 was used for statistical analysis. Heterogeneity was assessed by Cochran's Q test of heterogeneity and the I^2 index was used to quantify heterogeneity. In accordance with Higgins classification, I^2 values more than 0.7 were considered as high heterogeneity. The "metaprop" used for pooled prevalence calculation by using the random-effects model (Hallajzadeh et al. 2018; Hashemi et al. 2018; Hashemi et al. 2019; Hashemi et al. 2020; Pakzad et al. 2018). The exact method was used for standard error calculation. The meta-regression analysis was used to examine the effect of age, gender, sample size, and publication date as factors affecting heterogeneity among studies. The "metabias" command was used to check the publication bias, and if there was any publication bias, the prevalence rate was adjusted with the "metatrim" command using trim-and-fill method (Hallajzadeh et al. 2018; Hashemi et al. 2018; Hashemi et al. 2019; Hashemi et al. 2020; Pakzad et al. 2018). In all analysis a significance level of 0.05 was considered.

Results

Search results and study population

A total of 1995 studies were retrieved from different databases and 681 studies obtain after remove duplicate papers. Due to the screening, 14 studies were included (the detail are illustrated in Figure 1).

The patient's population in all 14 included studies was 3148 COVID-19 patients. The age was ranged from 19 to 95 years. The study setting assessment indicates 9 (64%) of the studies are Case series and 3 (21%) cross-sectional. The geographical location of the conducted studies indicated, 3 (21%) from China, 3 (21%) Italy and 2 (14.2%) USA. Other data is summarized in Table 2.

Clinical presentations

By the assessment of 14 included studies, the CNS or mental associated disorders in all population study were listed in Table 1. Figure 2 and Table 3 are shown pool prevalence of symptoms/psychiatric disorders/psychology.

According to this, the pooled prevalence of CNS or mental associated disorders with 95% CI was 50.68% (6.68–93.88). The most prevalence symptoms were hyposmia/anosmia/olfactory dysfunction (number of study: 10) with 36.20% (14.99–60.51). Only one study reported numbness/paresthesia and dysphonia. Pooled prevalence of numbness/paresthesia and dysphonia was 5.83% (2.17–12.25) and 2.39% (10.75–14.22); respectively. The pooled prevalence of depression and anxiety was 3.52% (2.62–4.54) and 13.92% (9.44–19.08). The pooled prevalence of the other disorders has been shown in Figure 2 and Table 3.

Heterogeneity and meta-regression

The Table 3 presents the results of the heterogeneity. According to Cochran's Q test of heterogeneity, there was significant heterogeneity among studies for all outcomes except confusion, sleep disorder/drowsiness, delirium, dysphonia (because there was only 1 study for this sub group), auditory dysfunction and numbness/paresthesia (because there was only 1 study for this sub group) and Auditory dysfunction. The I^2 index for most outcomes (including mental disorder, depression, anxiety, fatigue/weakness, CVD/NSD, headache/dizziness, hyposmia/anosmia/OD and dysgeusia/ageusia) was up to 80%. According to meta-regression results, the age had the significant effect on hyposmia/anosmia/OD prevalence; so that by increasing age, prevalence of hyposmia/anosmia/OD (coefficient: –2.81; p: 0.025) decreased significantly

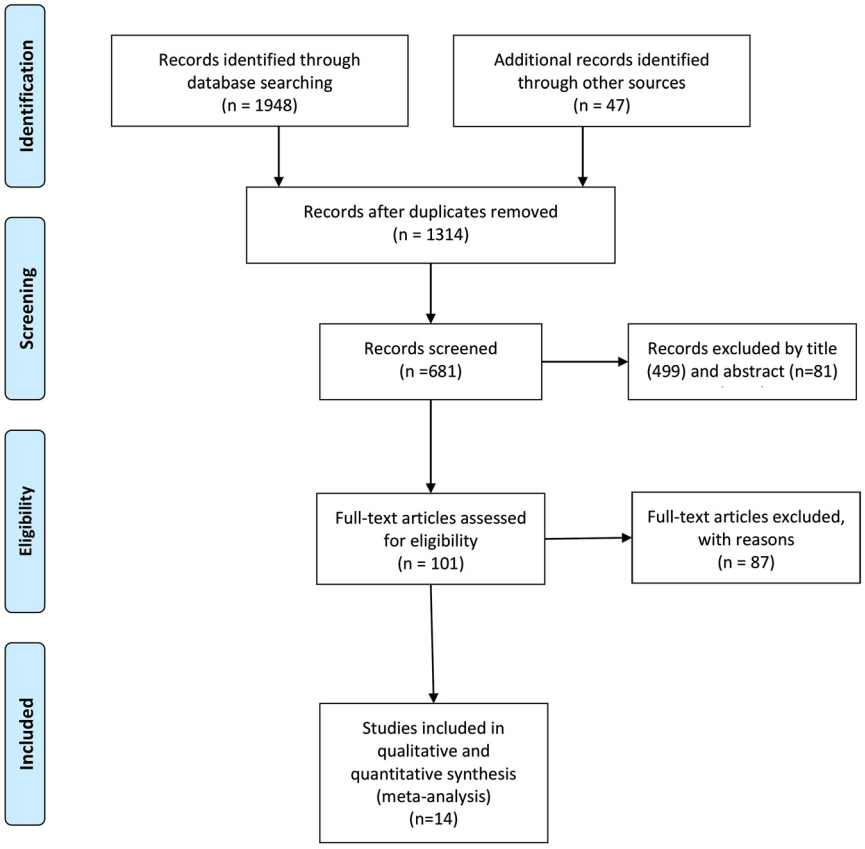

Figure 1: Follow diagram of systematic review and meta-analysis.

(Figure 3). For other outcomes the age has no effect on heterogeneity.

Publication bias

Based on the results of Egger's test, there is no significant publication bias in our meta-analysis.

Discussion

The aim of the current review and meta-analysis was to systematically review the COVID-19 associated central nervous system manifestations and neurological symptoms. Due to the screening and inclusion criteria 14 studies with 3148 sample size were assessed. Neurological symptoms in COVID-19 patients were reported from USA, China, Switzerland, Italy, UK, Netherland, Europe and Iran (Table 2). The current study result indicated that, the pooled prevalence of CNS or mental associated disorders with 95% CI was 50.68% (6.68–93.88). The most prevalence symptoms were hyposmia/anosmia/olfactory dysfunction with 36.20% (14.99–60.51), numbness/paresthesia 5.83% (2.17–12.25), dysphonia 2.39% (10.75–14.22), depression 3.52% (2.62–4.54) and anxiety 13.92% (9.44–19.08). Dysphonia and numbness or paresthesia was only seen in Europe and Italy in 39.17 ± 12.09 and 55 ± 14.65 ages (Range) respectively (Lechien et al. 2020; Liguori et al. 2020).

Neurological disease have reported in some respiratory viruses such as RSV (Bohmwald et al. 2018; Halfhide et al. 2011), influenza A and B (Xu et al. 1998) and enterovirus D68 (Imamura et al. 2014). The viruses can be detected in blood and they may use circulatory system to reach the CNS (Desforges et al. 2020). Respiratory syncytial virus (RSV) is a cause of lower respiratory tract infection in infects and children. The virus classified in the Orthopneumovirus genus (Walker et al. 2019). There are evidences due to the RSV neuroinvasive properties (Antonucci et al. 2010; Bohmwald et al. 2018; Nair et al. 2010). The RSV neurological manifestations could be including convulsions, febrile seizures and different types of encephalopathy and ataxia (Picone et al. 2019; Wallace and Zealley 1970). Also, human metapneumovirus (hMPV) is a respiratory pathogen and sporadically can induce seizures, encephalitis and encephalopathies (associated with epileptic symptoms) (Fernández et al. 2012; Wallace and Zealley 1970). Most influenza virus infections are limited to the upper respiratory tract but also its complications can involve the CNS (Kuiken and Taubenberger 2008; Popescu et al. 2017). Several studies have demonstrate that

Table 2: Characteristic of included studies of COVID-19 associated central nervous system manifestations and neurological symptoms.

Author	Country	Year	Study Design	Age (Range)	SS	Dementia as comorbidity	Confusion	Depression	Anxiety	Fatigue/ Weakness	Sleep disorder/ Drowsiness	Delirium
Aggarwal et al. 2020	USA	2020	CA	67 (38–95)	16	–	–	–	–	8	–	–
Bhat et al. 2020	USA	2020	CA	54.5 ± 11.5	8	–	–	–	–	–	–	–
Chen et al. 2020	China	2020	CA	55.5 ± 13.1	99	–	9	–	–	–	–	–
Chen et al. 2020	China	2020	CA	47.5	145	–	–	–	–	59	–	–
Hung et al. 2020	China	2020	CS	32–62	127	–	–	–	–	–	–	–
Speth et al. 2020	Switzerland	2020	CS	46.8 ± 15.9	103	–	–	–	–	–	–	–
Bianchetti et al. 2020	Italy	2020	CA	70.7 ± 12.9	627	82	–	–	–	–	–	55
Liguori et al. 2020	Italy	2020	CS	55 ± 14.65	103	–	23	39	34	33	51	–
Mao et al. 2020	China	2020	CA	52.7 ± 15.5	214	–	–	–	–	–	–	–
Lovell et al. 2020	UK	2020	CA	82 (72–89)	101	31	–	–	2	9	36	24
Tostmann et al. 2020	Netherlands	2020	CO	-	90	–	–	–	–	–	–	–
Lechien et al. 2020	Europe	2020	CS	39.17 ± 12.09	1420	–	–	36	–	–	–	–
Heidari et al. 2020	Iran	2020	CA	37.4	23	–	–	–	–	4	–	–
Gelardi et al. 2020	Italy	2020	CA	49.7 (19–70)	72	–	–	–	–	29	–	–

CVD	Headache/Dizziness	Dysphonia	Hyposmia/Anosmia/OD	Dysgeusia/Ageusia	Auditory dysfunction	Numbness/Paresthesia
2	4	–	3	3	–	–
–	–	–	1	1	–	–
40	8	–	–	–	–	–
–	29	–	–	–	2	–
2	6	–	5	–	–	–
–	–	–	63	67	–	–
–	–	–	–	–	–	–
–	40	–	40	48	2	6
6	36	–	11	12	–	–
–	–	–	–	–	–	–
–	64	–	37	–	–	–
13	998	176	997	770	–	–
–	–	–	19	–	–	–
–	16	–	34	34	–	–

CVD, Cerebrovascular disease; OD, Olfactory dysfunction; SS, Sample size; CA, Case series; CS, Cross-sectional; CO, Cohort.

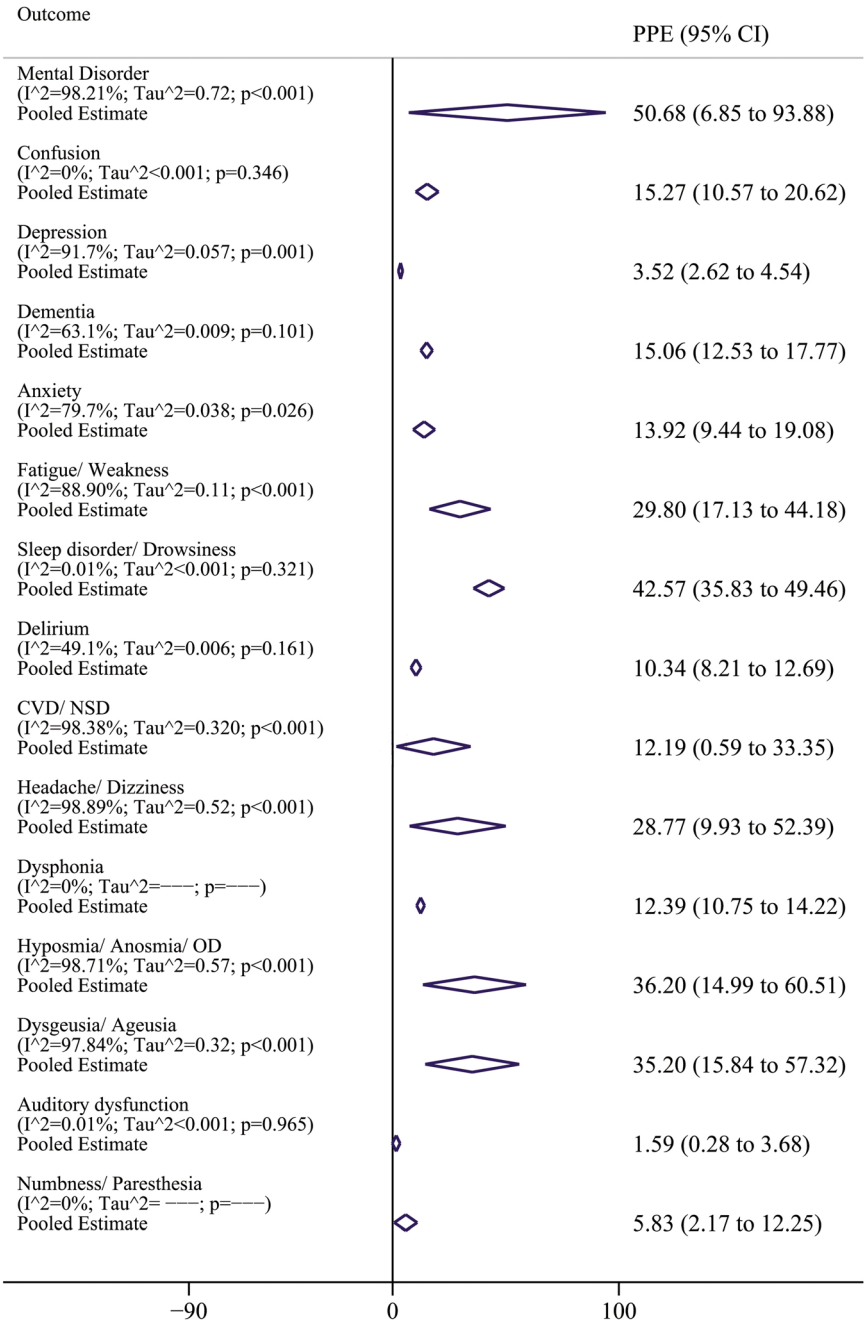

Figure 2: Pooled prevalence estimate (PPE) of psychiatry/psychology disorders/ symptoms in patients with COVID-19 based on the random effects model. The diamond mark illustrates the pooled prevalence estimate and length of diamond indicates 95% confidence interval. (CVD, Cerebrovascular disease; NSD, Nervous system disorders; OD, Olfactory dysfunction).

influenza A can be associated with encephalitis, Reye's syndrome, febrile seizure, Guillain–Barré syndrome, acute necrotizing encephalopathy and probably acute disseminated encephalomyelitis (Jang et al. 2009; Sivadon-Tardy et al. 2009; Zeng et al. 2013). The influenza a virus can also increasing the risk of Parkinson's disease developing (Jang et al. 2009; World Health Organization 2020). Recent investigations on suggested that, the influenza virus could induce experimental autoimmune encephalomyelitis (EAE), which reminds that recurrence of multiple sclerosis (MS) have been associated with viral infections (including influenza A) (Chen et al. 2017; Edwards et al. 1998). Various respiratory viruses have neurotropic features and can affect the nervous system, result in neuropathological outcomes, in the high-risk groups (Yachou et al. 2020). The MERS-CoV and the SARS-CoV can cause CNS symptoms such as neuroinvasive capabilities, Also the neurological manifestations have been seen in the SARS-CoV-2 infected patients (Yachou et al. 2020). HCoV-OC43 also is a coronavirus that can invade the CNS (Zubair et al. 2020). Seizures and encephalitis are common symptoms in the reviewed viruses except HCoV-OC43. Encephalitis,

Table 3: Pooled prevalence estimate and 95% confidence interval of psychiatry/psychology disorders/symptoms in patients with COVID-19.

Symptom	Heterogeneity	Number of studies	PPE%	95% CI
Mental disorder	I^2 = 98.21%; Tau^2 = 0.72; p < 0.001	3	50.68	(6.85–93.88)
Confusion	I^2 = 0%; Tau^2 < 0.001; p:0.346	2	15.27	(10.57–20.62)
Depression	I^2 = 91.7%; Tau^2 = 0.057; p:0.001	2	3.52	(2.62–4.54)
Anxiety	I^2 = 79.7%; Tau^2 = 0.038; p:0.026	2	13.92	(9.44–19.08)
Fatigue/weakness	I^2 = 88.90; Tau^2 = 0.11; p < 0.001	6	29.80	(17.13–44.18)
Sleep disorder/drowsiness	I^2 = 0.01%; Tau^2 < 0.001; p:0.321	2	42.57	(35.83–49.46)
Delirium	I^2 = 49.1%; Tau^2 = 0.006; p:0.161	2	10.34	(8.21–12.69)
CVD/ NSD	I^2 = 98.38%; Tau^2 = 0.320; p < 0.001	5	12.19	(0.59–33.35)
Headache/dizziness	I^2 = 98.89%; Tau^2 = 0.52; p < 0.001	9	28.77	(9.93–52.39)
Dysphonia	I^2 = 0% ; Tau^2 = -; p = -	1	12.39	(10.75–14.22)
Hyposmia/anosmia/OD	I^2 = 98.71%; Tau^2 = 0.57; p < 0.001	10	36.20	(14.99–60.51)
Dysgeusia/ageusia	I^2 = 97.84%; Tau^2 = 0.32; p < 0.001	7	35.20	(15.84–57.32)
Auditory dysfunction	I^2 = 0.01%; Tau^2 < 0.001; p:0.965	2	1.59	(0.28–3.68)
Numbness/paresthesia	I^2 = 0%; Tau^2 = -; p = -	1	5.83	(2.17–12.25)

CVD, Cerebrovascular disease; NSD, Nervous system disorders; OD, Olfactory dysfunction; CI, Confidence interval; PPE, Pooled prevalence estimate.

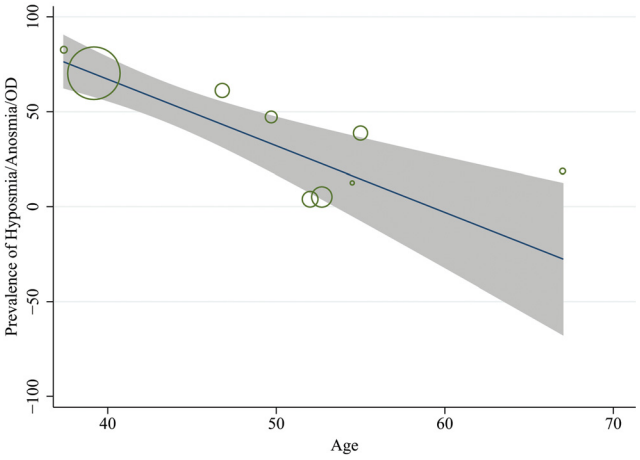

Figure 3: The association among prevalence of headache/dizziness (A) and hyposmia/anosmia/olfactory dysfunction (B) with age by means of meta-regression. Size of circles indicates the precision of each study. There is significant association with respect to prevalence of headache/dizziness and hyposmia/anosmia/olfactory dysfunction with age. The prevalence has been significantly decreased with increases of age in this survey.

confusion, fatigue, headache, ataxia, dizziness, anosmia and Guillain–Barré syndrome are mental symptoms of COVID-19 that are common symptoms in above viruses.

One of the frequent complications of COVID-19 patient with neurologic disorders was cerebrovascular problems among which acute ischemic cerebrovascular accident was the most frequent. A rare neurologic complication caused by cytokine storm and damage to the blood-brain barrier is acute necrotizing encephalopathy (ANE), It is more common associated with influenza but SARS-CoV-2 has also been associated with this condition (Reshef et al. 2014; Rossi 2008). Guillain-Barré Syndrome (GBS) is another complication of SARS-CoV-2 that reported in 5 cases in Italy and 2 cases from Wuhan, China (Toscano et al. 2020; Zhao et al. 2020). Hemophagocytic lymphohistiocytosis (HLH) is the next complication which often observes in hematologic malignancy, immunosuppression, or critical infections but has also been described in patients with SARS-CoV-2 (Al-Samkari and Berliner 2018).

Many drugs used for COVID-19 patients treating such as antivirals (e.g., remdesivir, ribavirin, lopinavir/ritonavir, favipiravir), biologic agents (tocilizumab) and antimalarials (hydroxychloroquine, chloroquine). Remdesivir is a nucleotide-analog inhibitor of RNA polymerases and neurologic effects and medication interactions of it is unknown (Wang et al. 2020). Ribavirin is RNA and DNA virus replication inhibitor and interferon alpha have neuropathic and neuropsychiatric sequelae (Fried and Russo 2003; Sleijfer et al. 2005). Chloroquine and hydroxychloroquine are endosomal/organelle pH modifications which correlate with neuropsychiatric side effects, ataxia and seizures. Methylprednisolone have an inflammation reduction mechanism and correlates with delirium (Bridwell et al. 2020). Ribavirine also used for SARS-CoV in patients with seizure, anosmia, myalgia and GTC (Hung et al. 2003; Hwang 2006; Lau et al. 2004). Intravenous immunoglobulin (IVIg), methylpred nisolone, ribavarin, convalescent serum and low molecular weight heparin (LMWH) use for loss of consciousness treating in SARS-CoV patients (Umapathi et al. 2004). Tazocine use in MERS-CoV patient for headache, dizziness, and intracerebral hemorrhage treating (Algahtani et al. 2016). Ribavirine and methylprednisolone also usage in therapy of intracerebral hemorrhage in MERS-CoV patients (Al-Hameed 2017). Interferon α2a, Ribavirin, and Lopinavir/

Ritonavir use in Guillain–Barré syndrome, acute sensory neuropathy, headache, Confusion and seizure treating of MERS-CoV (Kim et al. 2017).

Our results indicated that COVID-19 could represent neurological and mental manifestations. The current study result shows that, headache and dizziness are the most prevalence neurological symptoms in adults in Netherlands and Europe (Lechien et al. 2020; Tostmann et al. 2020). By the assessment of all included studies, the Hypsomia, Anosmia or olfactory dysfunction was most frequent symptom. Other symptoms were headache or dizziness, dysgeusia or ageusia, dysphonia, fatigue, cerebrovascular disease, delirium and sleep disorder or drwosiness. Also, other less frequent symptoms were includes depression, anxiety, and confusion, auditory dysfunction and numbness or paresthesia. The headache as one of the most common neurologic symptoms in COVID-19 was reported earlier. Also, it's reported that headache can be found in the early stages of the disease (Pinzon et al. 2020). In another studies headache was the most prevalence after myalgia (Nepal et al. 2020; Wang et al. 2020). Neurologic symptoms in SARS-CoV and MERS-CoV are included anxiety, depressed mood, insomnia and exacerbation of a panic disorder. According to studies delirium is common in SARS and MERS (Rogers et al. 2020). All of the mentioned highlights the importance of further investigations for the assessment of neurologic, CNS and mental symptoms in COVID-19 patients.

Our study had some strong points. We do an extensive search in different data-base to achieve of a large number of articles. Also this was the first study that used a meta-regression analysis to identify the determinants of heterogeneity that is novelty of our study. However, our study had some weakness. The major limitation of the current study was the limited number in primary studies in this particular field. Also most of the studies that included in this review came from low to moderate quality studies because have low sample size and case series design.

Conclusion

Our findings demonstrate that COVID-19 has a certain relation with neurological symptoms. the hypsomia, anosmia or olfactory dysfunction was most frequent symptom. Other symptoms were headache or dizziness, dysgeusia or ageusia, dysphonia, fatigue, cerebrovascular disease, delirium, and sleep disorder or drowsiness. Oder less frequent symptoms were includes depression, anxiety, and confusion, auditory dysfunction and numbness or paresthesia. Moreover, knowledge about mental disorders in COVID-19 patients in different ages and region is a step forwards to better knowledge for the COVID-19 disease progression and treating patients.

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References

Abiodun, O. and Ola, M. (2020). Role of brain renin angiotensin system in neurodegeneration: an update. Saudi J. Biol. Sci. 27: 905–912.

Aggarwal, S., Garcia-Telles, N., Aggarwal, G., Lavie, C., Lippi, G., and Henry, B.M. (2020). Clinical features, laboratory characteristics, and outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19): early report from the United States. Diagnosis 7: 91–96.

Al-Hameed, F. (2017). Spontaneous intracranial hemorrhage in a patient with Middle East respiratory syndrome corona virus. Saudi Med. J. 38: 196–200.

Al-Obaidi, M., Bahadoran, A., Wang, S., Manikam, R., Raju, C., and Sekaran, S. (2018). Disruption of the blood brain barrier is vital property of neurotropic viral infection of the central nervous system. Acta Virol. 62: 16–27.

Al-Samkari, H. and Berliner, N. (2018). Hemophagocytic lymphohistiocytosis. Annu. Rev. Pathol. 13: 27–49.

Algahtani, H., Subahi, A., and Shirah, B. (2016). Neurological complications of Middle East respiratory syndrome coronavirus: a report of two cases and review of the literature. Case. Rep. Neurol. Med. 2016: 3502683.

Antonucci, R., Chiappe, S., Porcella, A., Rosatelli, D., and Fanos, V. (2010). Bronchiolitis-associated encephalopathy in critically-ill infants: an underestimated complication? J. Matern. Fetal Neonatal Med. 23: 431–436.

Bhat, R., Hamid, A., Kuni, J., Saboo, S.S., Batra, K., Baruah, D., and Bhat, A. (2020). Chest imaging in patients hospitalized with COVID-19 infection – a case series. Curr. Probl. Diagn. Radiol. 49: 294–301.

Bianchetti, A., Rozzini, R., Guerini, F., Boffelli, S., Ranieri, P., Minelli, G., Bianchetti, L., and Trabucchi, M. (2020). Clinical presentation of COVID-19 in dementia patients. J. Nutr. Health Aging 24: 560–562.

Bohmwald, K., Galvez, N., Ríos, M., and Kalergis, A. (2018). Neurologic alterations due to respiratory virus infections. Front. Cell. Neurosci. 12: 386.

Bridwell, R., Long, B., and Gottlieb, M. (2020). Neurologic complications of COVID-19. Am. J. Emerg. Med. 38: 1549.e1543–1549.e1547.

Carlos, W., Dela, C., Cao, B., Pasnick, S., and Jamil, S. (2020). Novel Wuhan (2019-nCoV) coronavirus. Am. J. Respir. Crit. Care Med. 201: P7–P8.

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Ha, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., et al. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395: 507–513.

Chen, Q., Liu, Y., Lu, A., Ni, K., Xiang, Z., Wen, K., and Tu, W. (2017). Influenza virus infection exacerbates experimental autoimmune encephalomyelitis disease by promoting type IT cells infiltration into central nervous system. J. Autoimmun. 77: 1–10.

Chen, Q., Zheng, Z., Zhang, C., Zhang, X., Wu, H., Wang, J., Wang, S., and Zheng, C. (2020). Clinical characteristics of 145 patients with corona virus disease 2019 (COVID-19) in Taizhou, Zhejiang, China. Infection 48: 1–9.

Desforges, M., Le Coupanec, A., Dubeau, P., Bourgouin, A., Lajoie, L., Dubé, M., and Talbot, P. (2020). Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? Viruses 12: 1–28.

Edwards, S., Zvartau, M., Clarke, H., Irving, W., and Blumhardt, L. (1998). Clinical relapses and disease activity on magnetic resonance imaging associated with viral upper respiratory tract infections in multiple sclerosis. J. Neurol. Neurosurg. Psychiatr. 64: 736–741.

Ellul, M., Benjamin, L., Singh, B., Lant, S., Michael, B., Kneen, R., Defres, S., Sejvar, J., and Solomon, T. (2020). Neurological associations of COVID-19. Lancet Neurol. 19: 767–783.

Fernández, I., Polo, M., Muñoz-Almagro, C., Carretero, L., Ureña, S., Muñoz, A., Roura, R., and Dueñas, B. (2012). Human metapneumovirus in the cerebrospinal fluid of a patient with acute encephalitis. Arch. Neurol. 69: 649–652.

Fried, M. and Russo, M. (2003). Side effects of antiviral therapy for hepatitis C. Gastroenterology 124: 1711–1719.

Gelardi, M., Trecca, E., Cassano, M., and Ciprandi, G. (2020). Smell and taste dysfunction during the COVID-19 outbreak: a preliminary report. Acta Biomed. 91: 230–231.

Grifoni, A., Sidney, J., Zhang, Y., Scheuermann, R.H., Peters, B., and Sette, A. (2020). A sequence homology and bioinformatic approach can predict candidate targets for immune responses to SARS-CoV-2. Cell Host Microbe 27: 671–680.e672.

Halfhide, C.P., Flanagan, B.F., Brearey, S.P., Hunt, J.A., Fonceca, A.M., McNamara, P.S., Howarth, D., Edwards, S., and Smyth, R.L. (2011). Respiratory syncytial virus binds and undergoes transcription in neutrophils from the blood and airways of infants with severe bronchiolitis. J. Infect. Dis. 204: 451–458.

Hallajzadeh, J., Khoramdad, M., Izadi, N., Karamzad, N., Almasi-Hashiani, A., Ayubi, E., Qorbani, M., Pakzad, R., Hasanzadeh, A., and Sullman, M.J. (2018). Metabolic syndrome and its components in premenopausal and postmenopausal women: a comprehensive systematic review and meta-analysis on observational studies. Menopause 25: 1155–1164.

Hashemi, H., Pakzad, R., Heydarian, S., Yekta, A., Aghamirsalim, M., Shokrollahzadeh, F., Khoshhal, F., Pakbin, M., Ramin, S., and Khabazkhoob, M. (2019). Global and regional prevalence of strabismus: a comprehensive systematic review and meta-analysis. Strabismus 27: 54–65.

Hashemi, H., Pakzad, R., Yekta, A., Aghamirsalim, M., Pakbin, M., Ramin, S., and Khabazkhoob, M. (2020). Global and regional prevalence of age-related cataract: a comprehensive systematic review and meta-analysis. Eye 34: 1357–1370.

Hashemi, H., Pakzad, R., Yekta, A., Bostamzad, P., Aghamirsalim, M., Sardari, S., Valadkhan, M., Pakbin, M., Heydarian, S., and Khabazkhoob, M. (2018). Global and regional estimates of prevalence of amblyopia: a systematic review and meta-analysis. Strabismus 26: 168–183.

Heidari, F., Karimi, E., Firouzifar, M., Khamushian, P., Ansari, R., Mohammadi Ardehali, M., and Heidari, F. (2020). Anosmia as a prominent symptom of COVID-19 infection. Rhinology 58: 302–303.

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T.S., Herrler, G., Wu, N.H., Nitsche, A., and Ma, M. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181: 271–280.e278.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., et al. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395: 497–506.

Hung, E.C., Chim, S.S., Chan, P.K., Tong, Y.K., Ng, E.K., Chiu, R.W., Leung, C.-B., Sung, J.J., Tam, J.S., and Lo, Y.D. (2003). Detection of SARS coronavirus RNA in the cerebrospinal fluid of a patient with severe acute respiratory syndrome. Clin. Chem. 49: 2108–2109.

Hung, I.F., Lung, K.C., Tso, E.Y., Liu, R., Chung, T.W., Chu, M.Y., Ng, Y.Y., Lo, J., Chan, J., Tam, A.R., et al. (2020). Triple combination of interferon β-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet 395: 1695–1704.

Hwang, C.S. (2006). Olfactory neuropathy in severe acute respiratory syndrome: report of a case. Acta Neurol. Taiwan 15: 26–28.

Imamura, T., Suzuki, A., Lupisan, S., Kamigaki, T., Okamoto, M., Roy, C.N., Olveda, R., and Oshitani, H. (2014). Detection of enterovirus 68 in serum from pediatric patients with pneumonia and their clinical outcomes. Influenza Other Respir Viruses 8: 21–24.

Jang, H., Boltz, D., Sturm-Ramirez, K., Shepherd, K.R., Jiao, Y., Webster, R., and Smeyne, R.J. (2009). Highly pathogenic H5N1 influenza virus can enter the central nervous system and induce neuroinflammation and neurodegeneration. Proc. Natl. Acad. Sci. U.S.A. 106: 14063–14068.

Kim, J.E., Heo, J.H., Kim, H.O., Song, S.H., Park, S.S., Park, T.H., Ahn, J.Y., Kim, M.K., and Choi, J.P. (2017). Neurological complications during treatment of Middle East respiratory syndrome. J. Clin. Neurol. 13: 227–233.

Kuiken, T. and Taubenberger, J.K. (2008). Pathology of human influenza revisited. Vaccine 26(Suppl 4): D59–66.

Lau, K.K., Yu, W.C., Chu, C.M., Lau, S.T., Sheng, B., and Yuen, K.Y. (2004). Possible central nervous system infection by SARS coronavirus. Emerg. Infect. Dis. 10: 342–344.

Lechien, J.R., Chiesa-Estomba, C.M., Place, S., Van Laethem, Y., Cabaraux, P., Mat, Q., Huet, K., Plzak, J., Horoi, M., Hans, S., et al. (2020). Clinical and epidemiological characteristics of 1,420 European patients with mild-to-moderate coronavirus disease 2019. J. Intern. Med. 288: 335–344.

Li, Y.C., Bai, W.Z., and Hashikawa, T. (2020). The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J. Med. Virol. 92: 552–555.

Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gøtzsche, P.C., Ioannidis, J.P., Clarke, M., Devereaux, P.J., Kleijnen, J., and

Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J. Clin. Epidemiol. 62: e1–e34.

Liguori, C., Pierantozzi, M., Spanetta, M., Sarmati, L., Cesta, N., Iannetta, M., Ora, J., Genga Mina, G., Puxeddu, E., Balbi, O., et al. (2020). Subjective neurological symptoms frequently occur in patients with SARS-CoV2 infection. Brain Behav. Immun. 88: 11–16.

Lovell, N., Maddocks, M., Etkind, S.N., Taylor, K., Carey, I., Vora, V., Marsh, L., Higginson, I.J., Prentice, W., Edmonds, P., and Sleeman, K.E. (2020). Characteristics, symptom management, and outcomes of 101 patients with COVID-19 referred for hospital palliative care. J Pain Symptom 60: e77–e81.

Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., Chang, J., Hong, C., Zhou, Y., and Wang, D. (2020). Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 77: 683–690.

Michalicova, A., Bhide, K., Bhide, M., and Kovac, A. (2017). How viruses infiltrate the central nervous system. Acta Virol. 61: 393–400.

Nair, H., Nokes, D.J., Gessner, B.D., Dherani, M., Madhi, S.A., Singleton, R.J., O'Brien, K.L., Roca, A., Wright, P.F., and Bruce, N. (2010). Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet 375: 1545–1555.

Nepal, G., Rehrig, J.H., Shrestha, G.S., Shing, Y.K., Yadav, J.K., Ojha, R., Pokhrel, G., Tu, Z.L., and Huang, D.Y. (2020). Neurological manifestations of COVID-19: a systematic review. Crit. Care 24: 1–11.

Pakzad, R., Pakzad, I., Safiri, S., Shirzadi, M.R., Mohammadpour, M., Behroozi, A., Sullman, M.J., and Janati, A. (2018). Spatiotemporal analysis of brucellosis incidence in Iran from 2011 to 2014 using GIS. Int. J. Infect. Dis. 67: 129–136.

Picone, S., Mondì, V., Di Palma, F., Martini, L., and Paolillo, P. (2019). Neonatal encephalopathy and SIADH during RSV infection. Am. J. Perinatol. 36: S106–S109.

Pinzon, R.T., Wijaya, V.O., Buana, R.B., Al Jody, A., and Nunsio, P.N. (2020). Neurologic characteristics in coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. Front. Neurol. 11: 565.

Popescu, C.P., Florescu, S.A., Lupulescu, E., Zaharia, M., Tardei, G., Lazar, M., Ceausu, E., and Ruta, S.M. (2017). Neurologic complications of influenza B virus infection in adults, Romania. Emerg. Infect. Dis. 23: 574–581.

Ren, L.-L., Wang, Y.M., Wu, Z.Q., Xiang, Z.C., Guo, L., Xu, T., Jiang, Y.Z., Xiong, Y., Li, Y.J., and Li, X.W. (2020). Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chin. Med. J. 133: 1015–1024.

Reshef, R., Kreisel, T., Kay, D.B., and Yirmiya, R. (2014). Microglia and their CX3CR1 signaling are involved in hippocampal-but not olfactory bulb-related memory and neurogenesis. Brain Behav. Immun. 41: 239–250.

Rogers, J.P., Chesney, E., Oliver, D., Pollak, T.A., McGuire, P., Fusar-Poli, P., Zandi, M.S., Lewis, G., and David, A.S. (2020). Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatr. 7: 611–627.

Rossi, A. (2008). Imaging of acute disseminated encephalomyelitis. Neuroimaging Clin. 18: 149–161.

Sivadon-Tardy, V., Orlikowski, D., Porcher, R., Sharshar, T., Durand, M.-C., Enouf, V., Rozenberg, F., Caudie, C., Annane, D., and Van Der Werf, S. (2009). Guillain-Barré syndrome and influenza virus infection. Clin. Infect. Dis. 48: 48–56.

Sleijfer, S., Bannink, M., Van Gool, A.R., Kruit, W.H., and Stoter, G. (2005). Side effects of interferon-α therapy. Pharm. World Sci. 27: 423.

Soltani, S. (2020). The hemagglutinin-esterase gene in human coronaviruses SARS-CoV-2, HKU1 and OC43. Eur. Rev. Med. Pharmacol. Sci. 24: 6484–6485.

Soung, A. and Klein, R.S. (2018). Viral encephalitis and neurologic diseases: focus on astrocytes. Trends Mol. Med. 24: 950–962.

Speth, M.M., Singer-Cornelius, T., Obere, M., Gengler, I., Brockmeier, S.J., and Sedaghat, A.R. (2020). Olfactory dysfunction and sinonasal symptomatology in COVID-19: prevalence, severity, timing, and associated characteristics. Otolaryngol. Head Neck Surg. 163: 114–120.

Toscano, G., Palmerini, F., Ravaglia, S., Ruiz, L., Invernizzi, P., Cuzzoni, M.G., Franciotta, D., Baldanti, F., Daturi, R., and Postorino, P. (2020). Guillain–Barré syndrome associated with SARS-CoV-2. N. Engl. J. Med. 382: 2574–2576.

Tostmann, A., Bradley, J., Bousema, T., Yiek, W.K., Holwerda, M., Bleeker-Rovers, C., Ten Oever, J., Meijer, C., Rahamat-Langendoen, J., Hopman, J., et al. (2020). Strong associations and moderate predictive value of early symptoms for SARS-CoV-2 test positivity among healthcare workers, The Netherlands, March 2020. Euro Surveill. 25: 2000508.

Tsivgoulis, G., Palaiodimou, L., Katsanos, A.H., Caso, V., Köhrmann, M., Molina, C., Cordonnier, C., Fischer, U., Kelly, P., and Sharma, V.K. (2020). Neurological manifestations and implications of COVID-19 pandemic. Ther. Adv. Neurol. Disord. 13: 1–14.

Umapathi, T., Kor, A.C., Venketasubramanian, N., Lim, C.T., Pang, B.C., Yeo, T.T., Lee, C.C., Lim, P.L., Ponnudurai, K., and Chuah, K.L. (2004). Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). J. Neurol. 251: 1227–1231.

Walker, P.J., Siddell, S.G., Lefkowitz, E.J., Mushegian, A.R., Dempsey, D.M., Dutilh, B.E., Harrach, B., Harrison, R.L., Hendrickson, R.C., and Junglen, S. (2019). Changes to virus taxonomy and the international code of virus classification and nomenclature ratified by the international committee on taxonomy of viruses (2019). Arch. Virol. 164: 2417–2429.

Wallace, S.J. and Zealley, H. (1970). Neurological, electroencephalographic, and virological findings in febrile children. Arch. Dis. Child. 45: 611–623.

Wang, M., Guo, L., Chen, Q., Xia, G., and Wang, B. (2020). Typical radiological progression and clinical features of patients with coronavirus disease 2019. Aging 12: 7652–7659.

Wang, W., Tang, J., and Wei, F. (2020). Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. J. Med. Virol. 92: 441–447.

Wang, Y., Zhang, D., Du, G., Du, R., Zhao, J., Jin, Y., Fu, S., Gao, L., Cheng, Z., Lu, Q., and Hu, Y. (2020). Remdesivir in

adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 395: 1569–1578.

Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., and Tugwell, P. (1999). *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. Clinical Epidemiology Unit, University of Ottawa, Ottawa.

Wiersinga, W.J., Rhodes, A., Cheng, A.C., Peacock, S.J., and Prescott, H.C. (2020). Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. J. Am. Med. Assoc. 324: 782–793.

World Health Organization. (2020). Coronavirus disease 2019 (COVID-19). World Health Organization, Available at: www.who.int/docs/default-source/coronaviruse/weekly-updates (Accessed 9 September 2020).

Wright, E.J., Brew, B.J., and Wesselingh, S.L. (2008). Pathogenesis and diagnosis of viral infections of the nervous system. Neurol. Clin. 26: 617–633.

Xu, H., Yasui, O., Tsuruoka, H., Kuroda, K., Hayashi, K., Yamada, A., Ishizaki, T., Yamada, Y., Watanabe, T., and Hosaka, Y. (1998). Isolation of type B influenza virus from the blood of children. Clin. Infect. Dis. 27: 654–655.

Yachou, Y., El Idrissi, A., Belapasov, V., and Benali, S.A. (2020). Neuroinvasion, neurotropic, and neuroinflammatory events of SARS-CoV-2: understanding the neurological manifestations in COVID-19 patients. Neurol. Sci. 41: 1–3.

Zeng, H., Quinet, S., Huang, W., Gan, Y., Han, C., He, Y., and Wang, Y. (2013). Clinical and MRI features of neurological complications after influenza A (H1N1) infection in critically ill children. Pediatr. Radiol. 43: 1182–1189.

Zhao, H., Shen, D., Zhou, H., Liu, J., and Chen, S. (2020). Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? Lancet Neurol. 19: 383–384.

Zubair, A.S., McAlpine, L.S., Gardin, T., Farhadian, S., Kuruvilla, D.E., and Spudich, S. (2020). Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. JAMA Neurol. 77: 1018–1027.