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ORIGINAL RESEARCH

Characteristics of Patients with SARS-CoV-2 Positive Cerebrospinal Fluid: A Systematic Review

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Background: The coronavirus disease 2019 (COVID-19) has been shown to affect several systems, notably the respiratory system. However, there has been considerable evidence implicating the nervous system in COVID-19 infection. This study aims to investigate the clinical characteristics of patients whose cerebrospinal fluid (CSF) tested positive for SARS-CoV-2.

Methods: A comprehensive search of PubMed, EMBASE, Scopus, WHO Coronavirus database, bioRxiv, medRxiv, and Web of Science databases was carried out in August 2020. Original studies involving patients who tested positive for SARS-COV-2 in their CSF were included. Key search terms encompassed all variations of "COVID-19" AND "Cerebrospinal Fluid".

Results: A total of 525 studies were identified. Fifty-six full-text articles were assessed, of which 14 were included. In total, 14 patients tested positive for SARS-CoV-2 in their CSF. 21.4% (3/14) of patients had negative nasopharyngeal (NP) swabs despite a positive CSF sample. About 14.2% (2/14) of patients who initially had positive NP swabs developed neurological deterioration after a supposed recovery as indicated by their negative NP swabs, but their CSF still tested positive for SARS-CoV-2. Common symptoms were headache (42.8%; 6/14), fever (35.6%; 5/14), vomiting (28.6%; 4/14), cough (28.6; 4/14), visual disturbances (28.6%; 4/14), diarrhea (21.4%; 3/14), and seizures (21.4%; 3/14). Four patients (28.6%) were admitted to ICU, one (7.14%) was admitted to a rehabilitation facility, and two (14.3%) died.

Conclusion: Physicians should be familiar with the presenting neurological features of COVID-19, and be aware that they can occur despite a negative NP swab. The results of this study are intended to aid in the development of informed guidelines to diagnose and treat COVID-19 patients with neurological manifestations.

Keywords: COVID-19, SARS-CoV-2, CNS, CSF, central nervous system, cerebrospinal fluid

Background

Coronavirus Disease 2019 (COVID-19) is a novel infectious disease capable of causing mild to severe illness, typically respiratory, in both humans and animals. The virus responsible for COVID-19, referred to as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), resides primarily in the respiratory tract and causes symptoms ranging from mild cough, sore throat, and nasal congestion to more severe respiratory distress. Recently, it has been shown to have additional neuro-invasive potential.[1] Infected patients globally have been reported to have headaches, paraesthesia, anosmia, ageusia, neuralgia, and dizziness.[2]

Additionally, several case reports and cohort studies have reported rare cases of meningoencephalitis, seizures, and immune-mediated neurological diseases.[3]

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SARS-CoV-2 can either infiltrate the peripheral nervous system (PNS) and migrate to the CNS or directly infect the CNS.[4] There are three postulated mechanisms of transmission of the SARS-CoV-2 virus via the PNS: the transcribial route, axonal transport, and trans-synaptic transfer, and hematogenous and/or lymphatic route.[5] The transcribial route involves a primary olfactory infection followed by infiltration into the subarachnoid space via the cribriform plates.[4,6] The axonal transport and trans-synaptic transfer hypothesis suggests that an initial infection of peripheral nerve terminals results in a migration of the virus, up the nervous system, to the trigeminal, olfactory, and/or vagus nerve.[4,6] It is important to note that both the gastrointestinal and the respiratory branches of the vagus nerve are susceptible to the infection.[7–10] An infection of the CNS may occur via direct contact of the SARS-CoV-2 virus with the brain microvascular endothelial cells. This in turn leads to extracellular virus release into the CNS parenchyma. Lastly, compromised tight junctions at the blood brain barrier or virally infected leukocytes may provide viral access to the CNS via endocytosis.[9,10] More research is needed to accurately map the neurologic pathogenesis of SARS-CoV-2, and how this may translate to clinical diagnosis, prognosis, and patient care.

Dealing with a pandemic of this magnitude requires rapid and effective diagnostic tools to help combat the disease as early as possible. The diagnostic tool most widely accepted is the reverse transcriptase polymerase chain reaction (RT-PCR), used on a nasopharyngeal (NP) sample.[11] Although SARS-CoV-2 RT-PCR is typically conducted on an NP swab, it can also be conducted on a cerebrospinal fluid (CSF) sample obtained from a lumbar puncture (LP).[12–14]

In order to best understand the pathophysiology of SARS-CoV-2 as it relates to neuropsychiatric manifestations, it is important to explore viral presence in the nervous system, and how this may correlate—if at all—with clinical presentation and outcomes. Thus, this systematic review aims to compile and synthesize primary studies that report on patients who tested positive for SARS-CoV-2 via their CSF sample. Our study investigates the unique clinical manifestations and characteristics of this patient cohort, along with relevant outcomes, disease progression and management. Furthermore, we hope our findings will help identify when to consider PCR CSF tests despite a negative NP swab test.[15] By exploring the CNS involvement in SARS-CoV-2, this can aid in the development of new guidelines to diagnose and treat COVID-19 patients with neurological involvement.

Methods

Eligibility

We included primary research papers (case reports, case studies, cohort studies, cross-sectional studies, randomised control trials, letters to the editor reporting primary findings) that investigated the clinical course, outcomes, prognosis, management, and characteristics of patients who tested positive for SARS-COV-2 in their CSF using RT-PCR test. Exclusion criteria included non-English articles, animal studies, and non-original articles (eg, editorials that did not contain original data).

Search Strategy

We conducted our search in PubMed NCBI, Excerpta Medica dataBASE, Scopus, WHO COVID-19 Global literature on coronavirus disease database, Biorxiv and Medrxiv, and Web of Science on August 24th, 2020 using the following search terms: ((“Cerebrospinal fluid” [Mesh]) OR (“CSF” OR “Cerebrospinal fluid” OR “Cerebral spinal fluid” OR “Cerebro-spinal fluid” OR “Lumbar puncture” OR “Spinal tap”)) AND (“coronavirus” [MeSH] OR “coronavirus infections” [MeSH Terms] OR “coronavirus” [All Fields] OR “covid 2019” [All Fields] OR “SARS2” [All Fields] OR “SARS-CoV-2” [All Fields] OR “SARS-CoV -19” [All Fields] OR “severe acute respiratory syndrome coronavirus 2” [supplementary concept] OR “coronavirus infection” [All Fields] OR “severe acute respiratory pneumonia outbreak” [All Fields] OR “novel cov” [All Fields] OR “2019ncov” [All Fields] OR “sars cov2” [All Fields] OR “cov22” [All Fields] OR “ncov” [All Fields] OR “covid-19” [All Fields] OR “covid19” [All Fields] OR “coronaviridae” [All Fields] OR “corona virus” [All Fields]). The selection criteria were limited to papers published from December 2019 until August 2020 and papers written in English.

Study Selection

After deduplication of the titles, two reviewers independently screened all the titles and abstracts of the papers according to the predefined inclusion and exclusion criteria. Next, full texts of potentially eligible studies were retrieved and reviewed independently by two authors. A third author resolved any disagreement. Reviews that included patients who tested positive for SARS-CoV-2 in

their CSF were cross checked to identify any studies that matched our eligibility criteria.

Data Extraction and Interpretation

Data was extracted via a dual approach by two independent reviewers and inserted into a standardized review sheet. Data collected includes study characteristics (study title, authors, date of publication, publication type, study site, number of subjects), population characteristics, clinical findings, radiological findings, management, and final outcome. A third author resolved any disagreement.

Risk of Bias in Individual Studies

Two authors assessed the quality of the selected articles utilizing the National Institutes of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies. Quality assessment of case reports was carried out using Joanna Briggs Institute (JBI) critical appraisal checklist for case reports.

Meta-Analysis

A meta-analysis was not performed due to the preliminary nature of the study. Our aim was to review the literature in a scoping manner, and systemically gather and report the relevant data in the literature. In addition, due to the qualitative, heterogenic narrative nature of the outcomes, and the limited number of case reports (and absence of clinical studies), a meta-analysis would not be appropriate.

Results

Study Selection

An initial search of seven databases yielded a total of 525 publications. Fifty-six full-text articles were included and assessed for eligibility post abstract screening for relevance and deduplication, of which 14 were qualitatively analysed. After the application of the inclusion/exclusion criteria, they were narrowed down to 14. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram explaining the steps of identification, screening, inclusion, and exclusion is presented in Figure 1.

Study and Patients Characteristics

Of the 14 articles included in this study, nine were case reports,[10,16–23] three were retrospective studies,[24–26] one was a letter to the editor reporting original data of a patient,[27] and one follow-up letter to the editor of the same latter patient.[28] All were published in 2020. The studies were conducted worldwide, including France, USA, Spain, Brazil, Japan, Turkey, Sweden, UAE, France, Germany, and Iran (Table 1). From the 14 eligible studies identified, the total sample size was 733. Out of these, only 14 patients tested positive for SARS-CoV-2 in their CSF samples. As the scope of this review is to investigate only patients who tested positive for SARS-CoV-2 in their CSF according to the eligibility criteria, we only described these 14 patients. The mean age of the patients was 40 (SD ±15.7) and the median was 47.5, with 50% of them being females. Comorbidities were present in 40% (4/10) of the patients, and were mainly hypertension (2/4),[16,22] ischemic heart disease (1/4),[22] diabetes (1/4),[28] metastatic colorectal cancer (1/4),[22] migraines (1/4),[16] and one patient had prior pancreatic-kidney transplant surgery (1/4).[23]

Clinical Course and Diagnosis

In 21.4% (3/14) of cases, nasopharyngeal (NP) swabs initially tested negative despite a positive CSF sample.[10,17,18] 14.2% (2/14) of positive cases as per NP swab tested negative after supposed recovery but progressed to neurological deterioration and positive CSF tests.[20,22] 10/14 patients had both positive nasopharyngeal sample and CSF sample[16,19–25,28] (in two of these cases CSF was not tested initially, but was found to be positive at post-mortem), however samples were not always positive on the first test; 3/14 cases demonstrated a positive nasopharyngeal test but an initially negative CSF test.[20,22,28] Table 2 summarises the clinical and diagnostic findings.

Symptoms

Most commonly reported symptoms included: Headache (6/14),[10,16,17,19,21,28] fever (5/14),[17,20,21,23,28] vomiting (4/14),[16,21] cough (4/14),[10,19,21,23] visual disturbances (4/14),[16,19,23,28] diarrhoea (3/14),[18,21,23] and seizure (3/14)[17,23,28](Table 2). In two of the studies, the patients' COVID status was identified as severe[25,26] and in one of these cases the patient was noted to be suffering from acute respiratory distress syndrome.[25] Neurological symptoms were cited as the reason CSF test was carried out in 6/14 of the studies.[16–18,20,22,28]

Lab Findings

Studies of the positive patients' CSF samples (Table 3) revealed leukocytosis in 2/14 patients,[17,22] elevated CSF protein (hyperproteinorrachia) in 3/14,[22,23,28] hypoglycorrhachia in 1/14,[22] and an elevated red blood cells (RBCs) in 1/14 samples.[28] D-dimers were elevated in 3/14 blood samples.[16,21,22]

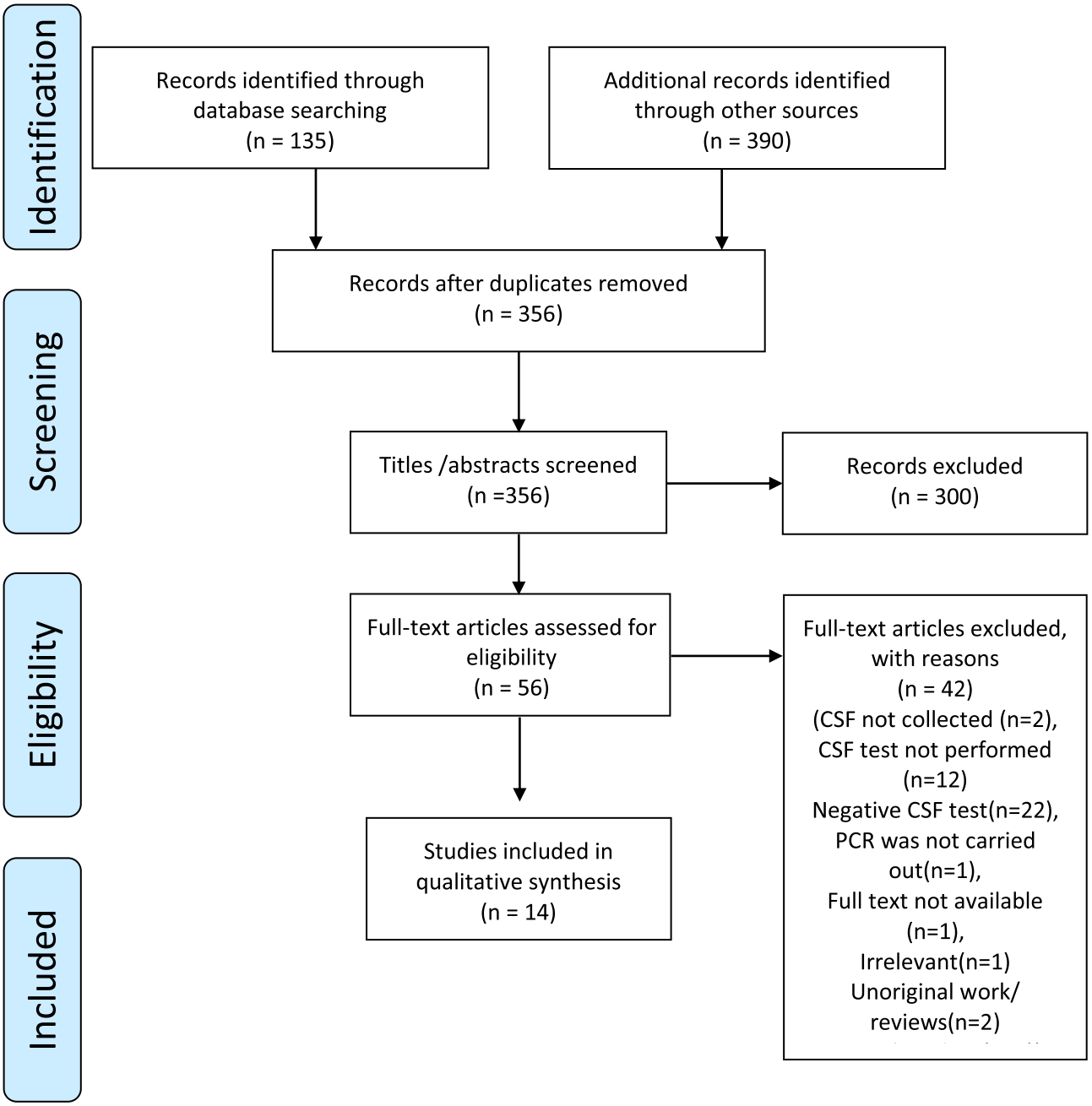

Figure 1 PRISMA flow diagram of literature search and selection.
Note: Adapted from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.[39]

Radiological Findings

Radiological findings (CXR, chest CT, systemic CT, Brain MRI, and head CT) were reported for 11/14 patients. However, we could not extract the data from one cohort study.[26] Radiological findings were normal in 2/14 patients.[18,28] The most common findings on brain MRI FLAIR were hyperintense regions in different areas of the brain (6/14),[10,17,19–21,23] and the commonest finding on chest CT was ground glass opacities in the lungs (5/14)[10,17,20,22,23] (Table 4).

EEG Findings

EEG findings were reported in two studies,[20,28] two of which noted a similar generalised slowing of waves with no epileptic activity.[20,28] One of these patients was noted to have a previous seizure.[28]

Table 1 Characteristics of Included Studies

Study	Authors	Country	Research Design	Sample Size	Number of CSF-Positive Cases	Gender	Age
1	Destras et al[24]	France	Retrospective Cohort Study	555	2	N/A	Adults
2	Huang et al[28]	USA	Case Report	1	1	F	40
3	Cebrián et al[16]	Spain	Case Report	1	1	F	74
4	Domingues et al[18]	Brazil	Case Report	1	1	F	42
5	Moriguchi et al[17]	Japan	Case Report	1	1	M	24
6	Fadakar et al[19]	Iran	Case Report	1	1	M	47
7	Demirci Otluoglu et al[10]	Turkey	Case Report	1	1	M	48
8	Helms et al[25]	French	Cohort Study	140	1	N/A	N/A
9	Rostami et al[20]	Sweden	Case Report	1	1	F	55
10	Al-olama et al[21]	UAE	Case Report	1	1	M	36
11	Mardani et al[22]	Iran	Case Report	1	1	F	64
12	Kremer et al[26]	France	Retrospective Cohort	28	1	N/A	N/A
13	Westhoff et al[23]	Germany	Case Report	1	1	M	69

Abbreviations: CSF, cerebrospinal fluid; N/A, not available; M, male; F, female.

Management and Treatment

The management of 4 patients was not discussed in their respective studies,[18,24–26] while the management for the remaining patients varied. Invasive intervention was required in two patients: Surgery was performed on 1/14 patients to remove the chronic subdural haematoma[21] and endotracheal intubation and mechanical ventilation was required on another patient with impaired consciousness.[17] The mainstay initial management in 4/14 patients was acyclovir.[10,20,22,28] This was, however, discontinued in one patient following negative herpes simplex virus results.[28] Levetiracetam was given in 3/14 patients[10,23,28] and hydroxychloroquine was administered to 5/14 patients.[10,16,22,23,28] Table 5 shows the management and outcomes of the 14 SARS-CoV-2 CSF positive patients.

Clinical Outcomes

The outcomes at the end of the study periods varied in these 14 SARS-CoV-2 CSF positive patients (Table 5). Overall, 2/14 deaths[24] and 4/14 ICU admissions[17,21,25] were reported. Symptoms improved in 1/14 cases who remained admitted,[10] while 6/14 cases were discharged/recovered,[16,18–20,23,28] and 1/14 was transferred to a rehabilitation centre.[20] Outcomes were not stated for two of the 14 patients.[22,26]

Risk of Bias Across Studies

Bias assessment is documented in Appendix 1, Tables S1 and S2.

Discussion

In this systematic review, we identified 14 articles which described 14 patients with positive SARS-CoV-2 CSF out of 733 articles. We systematically reviewed all reports of RT-PCR positive SARS-CoV-2 CSF samples in the literature since the start of the outbreak in December. A mixed-methods exploratory approach was adopted for data analysis, making observations, and investigating any preliminary patterns and theories that can be extracted from the sporadic cases reported. Common symptoms were headache fever, vomiting, cough, visual disturbances, diarrhoea, and seizures. Four patients were admitted to ICU, one was admitted to a rehabilitation facility, and two died.

The paucity of case reports that reported CSF-positive SARS-CoV-2 patients may indicate that viral neuroinvasion by SARS-CoV-2 appears to be rare. This is in

Table 2 Summary of Presentation and Clinical Course of All Cases Testing Positive for SARS-CoV-2 in CSF Samples

Study	Authors	NP Result	Positive CSF Result	General Signs	Neural Signs and Symptoms	Respiratory Symptoms
1	Destras et al[24]	Positive	2/555	N/A	N/A	N/A
2	Huang et al[28]	Positive	1	Fever; Lethargy	Headache; Seizures; Photophobia; Impaired consciousness; Neck stiffness	None
3	Cebrián et al[16]	Positive	1	Myalgia; Nausea; Vomiting	Headache; Photophobia; Visual disturbance (blurred binocular vision); Incoherent speech	None
4	Domingues et al[18]	Negative	1	Diarrhoea	Paresthesia and hypoesthesia of the left upper limb; Left hemithorax and hemiface	Common cold; Nasal obstruction
5	Moriguchi et al[17]	Negative	1	Fever; Fatigue	Headache; Seizures (transient generalised); Impaired consciousness	Sore throat
6	Fadakar et al[19]	Positive	1	Myalgia; Fatigue	Headache; Visual disturbances (saccade eye movements, optokinetic and end gaze rotational nystagmus); Gait disturbances; Vertigo	Cough
7	Demirci Otluoglu et al[10]	N/A	1	Myalgia; Fatigue	Headache; Neck stiffness; Anosmia	Cough
8	Helms et al[25]	Positive	1/140	N/A	N/A	Acute respiratory distress syndrome
9	Rostami et al[20]	Positive	1	Fever; Myalgia	Impaired brain stem reflexes	None
10	Al-olama et al[21]	Positive	1	Fever; Myalgia, Diarrhoea; Vomiting	Headache; Impaired consciousness	Cough; Pharyngitis
11	Mardani et al[22]	Positive	1	Generalised weakness	Impaired consciousness	Acute progressive dyspnoea
12	Kremer et al[26]	N/A	1/28	N/A	N/A	N/A
13	Westhoff et al[23]	Positive	1	Fever; Diarrhoea	Seizures (convulsive); Left-sided neglect	Cough

Abbreviations: N/A, not available; CSF, cerebrospinal fluid.

accordance with another systematic review in which 6%[17] tested positive out of 304 patients whose CSF was tested for SARS-CoV-2.[29]

The low prevalence of CSF positive SARS-CoV-2 results can be attributed to several factors, the first is that CSF testing rate was initially low since it is done only in cases with serious CNS manifestations, if patients had no CNS manifestations they would therefore not be tested. Secondly, isolation of SARS-CoV-2 in CSF may be challenging because of rapid CSF clearance, low titters or delayed sampling.[30–32] Further, CSF antibodies test was not always done for CSF negative patients which could

Table 3 Blood and Cerebrospinal Fluid Lab Findings of Cases with SARS-CoV-2 Positive CSF Samples

Study	Author	Laboratory Findings						
		CSF Sample				Blood Sample		
		RBC	WBC	Protein	Glu	WCC	Glu	CRP
1	Destras et al[24]	Data could not be extracted						
2	Huang et al[28]	↑	N/A	↑	*	↑ (100% lymphocytes)	*	N/A
3	Cebrián et al[16]	N/A	N/A	N/A	N/A	↑	N/A	↔
4	Domingues et al[18]	N/A	↔	↔	↔	N/A	N/A	↔
5	Moriguchi et al[17]	↔ None	↑ (10MN**, 2PMN***)	N/A	N/A	↑ (Neutrophil Predominant)	N/A	↑
6	Fadakar et al[19]	N/A	N/A	N/A	N/A	↔ (32% lymphocytes)	N/A	↔
7	Demirci Otluoglu et al[10]	N/A	↔	↔	↑	↔ (24.4% lymphocytes, 62.8% Neutrophils)	↑ 105mmol/L****	↔
8	Helms et al[25]	Data could not be extracted.						
9	Rostami et al[20]	N/A	N/A	N/A	N/A	↔/↑	N/A	↔/↑
10	Al-olama et al[21]	N/A	N/A	N/A	N/A	↑	↑	↔
11	Mardani et al[22]	N/A	↑ (90% polymorph)	↑	↓	↑ Polymorphs > lymphocytes	↑	N/A
12	Kremer et al[26]	Data could not be extracted.						
13	Westhoff et al[23]	N/A	↔ (100% lymphocytes)	↑	↔	↓ Lymphopenia	N/A	↑

Notes: *Units Not Reported, **Polymorphonuclear, ***Mononuclear. ****Non-fasting blood glucose.
Abbreviations: RBC, red blood cells; WBC, white blood cells; Glu, glucose; WCC, white cell count; CRP, C-reactive protein; N/A, not available; ↑, elevated levels; ↓, decreased levels; ↔, normal levels.

have led to missing resolved infection. In a recent systematic review, it was reported that out of those who did not test positive for CSF but had CNS symptoms, 42/58 (72%) tested positive for SARS-CoV-2 antibodies in the CSF.[29]

The discrepancy between CSF results and NP results could be attributed to the variability in the cycle threshold Ct (Ct; the number of amplification cycles required for the target gene to exceed the threshold) cut-off point (some used 40, some 37 and some 35).[17,29] Preanalytical issues such as collection techniques, and inadequate sample storage/transportation, timing of sample throughout the course of the disease which could have led to serious diagnostic errors.[33] Further, serum antibodies were not always checked for NP PCR negative patients which could have verified the resolved infections. Additionally, CSF SARS-CoV-2 PCR testing is not 100% specific for intrathecal virus, in part because a sample can be contaminated from shed airborne virus or blood contamination.[34] Interestingly, PCR testing for the N2 gene target of SARS-CoV-2 was noted to have the highest sensitivity in CSF when compared with a nasopharyngeal swab, bronchoalveolar lavage, sputum, plasma, or stool.[37] Despite this, the clinical indications for performing LPs in patients with SARS-CoV-2 infection remain unclear. Additionally, how clinicians can use information gained from LPs, such as cell counts and infectious workup, in the management of COVID-19 and neurological symptoms has not been established.

In this review, comorbidities were not commonly present among CSF positive patients (60%) which re-emphasizes that otherwise healthy individuals may present with CSF viral neuro-infiltration in the absence of comorbidities in the setting of COVID-19.[35]

Patients whose CSF samples tested positive for SARS-CoV-2 reported a range of symptoms, with respiratory distress not always being reported. Headache, fever,

Table 4 Radiological Findings of Cases with SARS-CoV-2 Positive CSF Samples

Study	Authors	Chest Findings	Brain MRI	Head CT
1	Destras et al[24]	N/A	N/A	N/A
2	Huang et al[28]	Unremarkable.	N/A	Unremarkable.
3	Cebrián et al[16]	Unremarkable.	Right parietal cortical-subcortical restricted diffusion	Unremarkable.
4	Domingues et al[18]	Unremarkable.	Unremarkable.	Unremarkable.
5	Moriguchi et al[17]	Ground glass opacities	Hyperintense lesions in the right mesial temporal lobe and hippocampus; Slight hippocampal atrophy.	Unremarkable.
6	Fadakar et al[19]	N/A	Bilateral cerebellar hemispheres and vermis hyperintensities; Edema; Cortical-meningeal enhancement of cerebellum	N/A
7	Demirci Otluoglu et al[10]	Ground glass opacities; Consolidation	Hyperintense lesions in the posterior medial cortical surface of the temporal lobe; Hyperintense lesions in the upper cervical spinal cord.	Unremarkable.
8	Helms et al[25]	N/A	N/A	N/A
9	Rostami et al[20]	Ground Glass opacities/ consolidations.	1st Brain MRI: Acute necrotizing encephalitis. 2nd Brain MRI: Partial regression of the changes in the brainstem and medial temporal lobes; More pronounced hyperintensities in central thalami and subinsular regions.	Symmetrical hypodensities in the thalami; Low attenuation areas in the thalami and midbrain.
10	Al-olama et al[21]	Unremarkable	Right frontal intracerebral hematoma; Subarachnoid hemorrhage in the ipsilateral sylvian fissure and frontal and temporal lobes; Acute subdural hematoma; Edema causing midline shift.	Hyperintensities in the bilateral supratentorial leptomeningeal area; Chronic right subdural hematoma; Re-reabsorbing intracerebral hematoma; Perilesional brain edema causing midline shift.
11	Mardani et al[22]	Bilateral Pleural effusion; Collapse consolidation of basal segments; Patchy ground-glass opacities	N/A	N/A
12	Kremer et al[26]	Data could not be extracted		
13	Westhoff et al[23]	Ground-glass opacities; Consolidation	Linear meningeal hyperintensities; White matter edema	N/A

vomiting, coughing, and visual disturbances were commonly reported, before progressing to more severe/intense neurological symptoms.[36] This might have an implication on CSF testing for diagnostic purposes. Further studies are required to define whether CSF SARS-CoV-2 testing is warranted in certain clinical contexts.[16,20,28]

Table 5 The Management and Outcomes of SARS-CoV-2 CSF Positive Patients

Study	Authors	Antivirals	Antibiotics	Antiepileptics	Other Medications	Outcomes
1	Destras et al[24]	N/A	N/A	N/A	N/A	Death (2)
2	Huang et al[28]	Acyclovir	Ceftriaxone/Vancomycin	Levetiracetam	HCQ	Full Recovery
3	Cebrián et al[16]	Lopinavir/ Ritonavir	Ceftriaxone	None	Pain drugs; Fluid replacement; Oxygen therapy; HCQ; Acetaminophen; Dexketoprofen; Acetylsalicylic acid	Discharged
4	Domingues et al[18]	N/A	N/A	N/A	N/A	Full recovery
5	Moriguchi et al[17]	Aciclovir; Favipiravir	Ceftriaxone; Vancomycin	Levetiraceta	Endotracheal intubation + Mechanical ventilation; Steroids	ICU
6	Fadakar et al[19]	Lopinavir; Ritonavir	None	None	None	Discharged
7	Demirci Otluoglu et al[10]	Favipiravir; Acyclovir	Piperacillin/Tazobactam	Levetiracetam	HCQ; Steroids	Stable under treatment
8	Helms et al[25]	N/A	N/A	N/A	N/A	ICU
9	Rostami et al[20]	Acyclovir	None	None	IVIG; Immunotherapy with plasma exchange	Discharged; Rehabilitation
10	Al-olama et al[21]		None	None	Burr hole	ICU
11	Mardani et al[22]	Lopinavir/ Ritonavir; Acyclovir	Ceftriaxone; Clindamycin; Meropenem; Vancomycin; Ampicillin	None	HCQ; Steroids; Folinic acid; Fluorouracil; Irinotecan	N/A
12	Kremer et al[26]	N/A	N/A	N/A	N/A	N/A
13	Westhoff et al[23]	None	None	Levetiracetam	Steroids; Insulin; Oxygen supply; Tacrolimus; HCQ	ICU → full recovery

Abbreviations: N/A, not available; HCQ, hydroxychloroquine; IVIG, intravenous immunoglobulin G; ICU, intensive care unit.

High levels of lymphocytes and protein were reported in 2/14 and 3/14 CSF samples of COVID-19 positive patients, respectively. CSF Pleocytosis is expected and occurs secondary to an inflammatory and/or infectious process.[29] Also, the observation of hyperproteinorrachia may indicate axonal injury and the existence of intrathecal antibodies.[29] There were no striking blood findings except for leucocytosis and hyperglycaemia. Both are expected and reflects the inflammatory process due to the disease. However, due to the lack of data, it is not known whether patients with hyperglycaemia in these case reports had pre-existing diabetes or not.

The EEG findings showed two patients with generalised slowing of waves with no epileptic activity. One of them had a history of pre-existing seizures. It is well documented in the literature that COVID-19 can result in EEG changes, and it is correlated with disease severity.[37,38] EEG findings in COVID-19 may indicate localized dysfunction, non-specific encephalopathy, and cortical irritability.[38] In fact, frontal findings are common and have been proposed as a biomarker for COVID-19 encephalopathy.[38] Diffuse EEG changes in the context of COVID-19 have been speculated to result from systemic involvement or diffuse viral

involvement of the brain while frontal EEG findings suggest direct brain involvement.[38]

There are several limitations to this review mainly attributed to lack of data from original case series such as description of test technique, time at which sample is collected, CSF analysis and SARS CoV antibodies. Lastly, this review is limited by publication bias and the paucity of published case reports.

More studies are needed to describe how results of LP influence clinical decision-making in a case series of patients with COVID-19 even if SARS-CoV-2 is not detected in the CSF.

Conclusions

This review describes the unique characteristics of patients who tested positive for SARS-CoV-2 in their CSF sample, regardless of the test outcome of the NP sample. Nevertheless, there are not enough data in the literature for guideline formation, especially given the fact that COVID-19 is a novel virus and an emergent crisis. Hence, more evidence is needed to improve our understanding regarding how results of LP influence clinical decision-making in a case series of patients with COVID-19 even if SARS-CoV-2 is not detected in the CSF. Additionally, how clinicians can use information gained from LPs, such as cell counts and infectious workup, in the management of COVID-19.

Abbreviations

COVID-19, coronavirus disease 2019; CSF, cerebrospinal fluid; NP, nasopharyngeal; RT-PCR, reverse transcriptase polymerase chain reaction; LP, Lumbar Puncture; PNS, peripheral nervous system; NIH, National Institutes of Health; JBI, Joanna Briggs Institute; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Data Sharing Statement

All data generated or analysed during this study are included in this published article and its supplementary information files.

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Author Contributions

MS conceived of the idea. MS, SIM, WK, LRM, and YA drafted one or more sections of the manuscript. MS, SIM, and GAJ reviewed and edited the manuscript. GAJ supervised the work. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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