Clinical features of SARS-CoV-2-associated encephalitis and meningitis amid COVID-19 pandemic

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Abstract

BACKGROUND
Since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic, numerous studies have been published on SARS-CoV-2–related encephalitis/meningitis, but it has not been established if there are specific clinical characteristics of encephalitis/meningitis associated with SARS-CoV-2 infection.

AIM
To identify the specific clinical features of cases of encephalitis/meningitis associated with SARS-CoV-2 infection in the context of this virus infection pandemic and investigate their relationship with SARS-CoV-2 infection.

METHODS
We searched PubMed, and included single case reports and case series with full text in English, reporting original data of coronavirus disease-19 (COVID-19) patients with encephalitis/meningitis and a confirmed recent SARS-CoV-2 infection. Clinical data were extracted.

RESULTS
We identified 22 articles (18 single case reports and 4 case series) reporting on a total of 32 encephalitis/meningitis patients with confirmed SARS-CoV-2 infection. SARS-CoV-2 infection was confirmed through reverse transcriptase-polymerase-chain-reaction (RT-PCR) in 96.88% of cases. A total of 22 (68.75%) patients had
symptoms of SARS-CoV-2 infection in about 1 wk (7.91 d) preceding the onset of neurologic symptoms. The most common neurological symptoms were consciousness disturbance (59.38%), seizure (21.88%), delirium (18.75%), and headache (18.75%). Four cases were confirmed by positive RT-PCR results in cerebrospinal fluid (CSF), one was confirmed by positive RT-PCR results in postoperative brain tissue, and one by the presence of SARS-CoV-2 antibodies in CSF. The mainly damaged targets identified by neuroimaging included the temporal lobe (15.63%), white matter (12.5%), frontal lobe (9.38%), corpus callosum (9.38%), and cervical spinal cord (9.38%). Eighty percent of patients had electroencephalograms that showed a diffuse slow wave. Twenty-eight (87.5%) patients were administered with specific treatment. The majority (65.63%) of patients improved following systemic therapy.

**CONCLUSION**

Encephalitis/meningitis is the common neurological complication in patients with COVID-19. The appropriate use of definitions and exclusion of potential similar diseases are important to reduce over-diagnosis of SARS-CoV-2 associated encephalitis or meningitis.

**Key Words:** COVID-19; SARS-CoV-2; Encephalitis; Meningitis; Clinical features; System review

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**Core Tip:** Since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic, although many cases or cases series of SARS-CoV-2-related encephalitis/meningitis have been reported, the specific clinical characteristics of SARS-CoV-2-related encephalitis/meningitis have not been systematically described. We retrospectively analyzed and summarized the comprehensive clinical characteristics of SARS-CoV-2-related encephalitis/meningitis, including demographic characteristics, diagnostic investigations, and outcomes.

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**INTRODUCTION**

Coronavirus disease-19 (COVID-19) is an illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In December 2019, the first coronavirus outbreak was detected in China, which quickly spread around the world and became a global health emergency[1]. As of November 4, 2020, there were over 47690000 confirmed COVID-19 cases and 1210000 reported deaths in 216 countries worldwide, according to the World Health Organization (WHO) report.

The Centers for Disease Control has termed that many cases feature multisystem inflammatory syndrome in the setting of SARS-CoV-2 positive diagnostic testing[2]. SARS-CoV-2 may cause severe neurological complications, such as encephalopathy, encephalitis, stroke, acute disseminated encephalomyelitis, Guillain Barré syndrome, and skeletal muscle involvement[3]. Up to 85% of patients with SARS-CoV-2 have minor neurological symptoms[4]. Up to 20% of patients with SARS-CoV-2 require admission to the intensive care unit (ICU) because of neurological problems, and these patients have a higher mortality[5]. Neurological symptoms of SARS-CoV-2 include headache, decreased responsiveness, anosmia, myalgia, ageusia, hypoguesia, or dysgeusia[6].

Encephalitis refers to acute, diffuse, inflammatory lesions in the brain parenchyma caused by pathogens, including neuronal damage and nerve tissue lesions. The common symptoms of encephalitis include headache, fever, vomiting, convulsions, focal neurologic deficits, and consciousness disorders[7]. Meningitis is an infection of
the meninges, and its clinical manifestations include fever, vomiting, headache, and meningeal symptoms. Cerebrospinal fluid (CSF) examination of meningitis usually shows changes in inflammation[9].

SARS-CoV-2 and SARS-CoV are very similar in structure, and both enter human cells after binding to the angiotensin converting enzyme 2 (ACE2) receptor. For this reason, ACE2-expressing cells, like neurons or glial cells, may be the target cells for SARS-CoV-2 infection[10]. Recently, Moriguchi et al[10] reported the first case of meningitis/encephalitis that was caused by SARS-CoV-2. The direct evidence for confirmation of SARS-CoV-2 associated encephalitis/meningitis was the detection of SARS-CoV-2 RNA in CSF[10]. There are possibly two principal routes for SARS-CoV-2 to affect the central nervous system (CNS): Hematogenous dissemination or retrograde dissemination of neurons via indirect routes. Nevertheless, the underlying neurotropic mechanism of SARS-CoV-2 has not yet been established[10-12].

The sensitivity of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) of SARS-CoV-2 to detect acute COVID-19 in appropriately treated nasopharyngeal swabs is high, but current data are limited to evaluate the sensitivity of this technique in CSF in patients with neurological disease[13]. Due to the time limit of transmission of COVID-19, its CSF titer may be extremely low, which makes it difficult to diagnose SARS-CoV-2-related encephalitis[13].

Since the SARS-CoV-2 epidemic, numerous studies have been published on SARS-CoV-2-related encephalitis/meningitis[14-16], but it has not been established if there are specific clinical characteristics of encephalitis/meningitis after SARS-CoV-2 based on published cases or case series. Therefore, we conducted a systematic and retrospective review of all published studies, which includes cases or case series, on SARS-CoV-2-related encephalitis/meningitis, and gave a comprehensive overview of clinical features, including demographic characteristics, diagnostic investigations, and outcomes, of SARS-CoV-2-related encephalitis/meningitis patients.

**MATERIALS AND METHODS**

We conducted a systematical search of the medical literature using MEDLINE (accessed from PubMed) and Google Scholar from December 01, 2019 to September 13, 2020 for related published articles. The types of literature included isolated case reports, case series, and cohort studies. We used search terms, “COVID-19 and encephalitis, meningitis” and “SARS-CoV-2 and encephalitis, meningitis”. Full-text articles were obtained from journals’ websites. We analysed demographics, neurological symptoms and signs, subtype, blood test, CSF, neuroimaging, electroencephalogram (EEG), treatment, and outcome characteristics of COVID-19 patients complicated with encephalitis/meningitis. We also described the pathogenesis of COVID-19-associated encephalitis and meningitis.

**RESULTS**

We identified 22 articles that were published between January 1, 2020 and September 13, including data from 30 isolated cases of confirmed COVID-19 patients complicated with encephalitis/meningitis. Tables 1 and 2 summarize the detailed demographic and clinical characteristics of patients with SARS-CoV-2-associated encephalitis/meningitis[15-19].

Of the 32 individual patients with SARS-CoV-2-associated encephalitis or meningitis, 20 (62.5%) were male, and 12 (37.5%) were female, with a male-to-female ratio of 1.67:1. Their median age was 45.37 years (age range, 8-75 years). A total of 31 (96.88%) definite cases of SARS-CoV-2 infection were those confirmed by positive RT-PCR results, and one (11.4%) case was confirmed by the presence of SARS-CoV-2 antibodies. The time between reported viral syndrome and confirmed COVID-19 was 6 d (range, 2-15 d). A total of 22 (68.75%) patients had symptoms of SARS-CoV-2 infection in about 1 wk (7.91 d) preceding the onset of neurological symptoms (Table 2). Fever (n = 16, 55.17%), cough (n = 13, 44.83%), and dyspnea (n = 11, 37.93%) were the most frequently documented initial symptoms of SARS-CoV-2 infection, followed by diarrhea (n = 4, 13.79%). Median time between reported viral syndrome and onset of neurological symptoms was 7.91 d (range, 1-21 d). Consciousness disturbance (n = 19, 59.38%), seizure (n = 7, 21.88%), delirium (n = 6, 18.75%), and headache (n = 6, 18.75%) were the most frequently documented neurological symptoms of SARS-CoV-2-associated encephalitis/meningitis, followed by altered
| No. | Ref. | Age/Sex | Area | Past medical history | Viral syndrome | Diagnosis of COVID-19 | TVC (d) | Neurological symptoms | Neurological signs | TVN (d) | Subtype | Primary target | Treatment | Outcome |
|-----|------|---------|------|----------------------|---------------|---------------------|-------|---------------------|------------------|-------|---------|--------------|-----------|---------|
| 1   | 16   | NA/male | China| N/A                  | Fever, shortness of breath, myalgia | (+) RT-PCR/PS | N/A | Consciousness confusion | (+) Meningeal irritation signs (including nuchal rigidity, Kernig sign and Brudzinski sign) | 14 | ME | N/A | Supportive therapy (mannitol infusion, oxygen therapy), arbidol | Good: Consciousness was completely clear, hospital discharged |
| 2   | 9    | 24 yr/male | Japan| N/A                  | Headache, fatigue, fever | (-) RT-PCR/NPS | N/A | Consciousness disturbance, seizures | (+) Neck stiffness | 9 | ME | N/A | N/A |
| 3   | 2    | 23 yr/male | Italy| Substance abuse | Psychomotor agitation, thought disorganization, persecutory delusions, auditory hallucinations, anxiety, insomnia | (+) RT-PCR/PS | N/A | Dysphagia, dyskinesias, autonomic instabilities | Non responsive to commands, non-verbal, despite being able to move all his extremities and reacting to noxious stimuli | 8 | E | N/A | High doses of DEX, IVlg | Good: Clinical conditions are ameliorating |
| 4   | 17   | 35 yr/female | Turkey| N/A                  | Mild flu-like complaints | (+) RT-PCR/PS | N/A | Headache, nausea, dizziness, seizure | N/A | 14 | E | Left anterior temporal lobe | Left anterior temporal lobectomy | Good: No post-operative neurological deficits, symptoms improved completely |
| 5   | 36   | 36 yr/male | United Arab Emirates| N/A                  | Fever, headache, myalgia, cough, diarrhea, vomiting | (+) RT-PCR/PS | 5 | Drowsiness, consciousness confusion | (+) Mild neck stiffness | 5 | ME | Supratentorial leptomeningeal, right frontal lobe | N/A | Poor: The patient’s neurological symptoms was not improved |
| 6   | 19   | 75 yr/male | Japan| Alzheimer’s disease | Diarrhea | (+) RT-PCR/PS | 6 | Left hand kinetic tremor, walking instability, urinary incontinence | (+) Finger-to-nose test; (+) ataxic gait was observed | 6 | E | Corpus callosum | Subbactam/ampicillin, favipiravir, corticosteroid pulse, ciclesonide, meropenem | Dead |
| 7   | 20   | 31 yr/female | United States| Sickle cell disease | Progressive dyspnea | (+) RT-PCR/NPS | 5 | Paralysis | Coma | 11 | EM | Hydroxychloroquine, peramivir | Dead |
| 8   | 20   | 34 yr/male | United States| Hypertension | Fever, shortness of breath, cough | (+) RT-PCR/NPS | 2 | Consciousness disturbance, myoclonus | Absent corneal and gag reflexes, absent withdrawal to painful | 9 | E | Corpus callosum | Hydroxychloroquine | N/A |

Table 1: Demographic and clinical characteristics of acute neurologic illness among patients with confirmed encephalitis/meningitis with evidence of severe acute respiratory syndrome coronavirus 2 infection
| Case | Age/sex | Country | Comorbidities | Symptoms | Testing | RA | Refle  | CNS | Therapy | Outcome |
|------|---------|---------|---------------|---------|--------|----|--------|-----|---------|---------|
| 1 | 80 yr/male | United States | Hypertension, COPD | Cough, fever, dyspnea, cough | (+) RT-PCR/NPS | N/A | Myoclonus | Absent oculocephalic reflex and withdrawal to pain, diminished deep tendon reflexes | Right temporal lobe | Hydroxychloroquine | Good: Hospital discharged without major neurologic sequelae |
| 2 | 72 yr/male | United States | N/A | Generalized weakness, fever | (+) RT-PCR/NPS | 3 | Status epilepticus | N/A | 3 | E | Frontal lobe | Anticonvulsant medications | Good: Recovery |
| 3 | 60 yr/female | Iran | Hypertension, diabetes | Fever, myalgia, dry cough | (+) Anti-SARS-CoV-2 IgM, IgG in serum | 10 | Drowsiness, decline consciousness, seizure, headaches | N/A | 10 | E | Temporal lobe, pontine, thalami | Broad-spectrum IV antibiotics, hydroxychloroquine, azithromycin, IVlg, levetiracetam, methylprednisolone | Good: Normal consciousness, no diplopia or other abnormal findings |
| 4 | 62 yr/female | Brazil | Dyspnea, headache | Coryza, nasal obstruction | (+) RT-PCR/NPS | N/A | Paresthesias (left upper limb, left hemithorax, and hemiface) | Hypoesthesia in left upper limb, left hemithorax, and hemiface | 21 | CM | Frontal lobe | Cervical spinal cord | Corticosteroids | Good: Recovery |
| 5 | 50 yr/male | United Kingdom | Hypertension, glaucoma | Fever, progressive dyspnea, cough, diarrhea | (+) RT-PCR/NPS | 11 | Unsteady gait, diplopia, oscillopsia, limb ataxia, altered sensation in right arm, hiccup and dribbling when eating or drinking | Facial weakness, reduced tongue movements, limb ataxia | 13 | CM | Brain stem; cervical spine | Gabapentin | Good: Neurological symptoms improved steadily and hospital discharged |
| 6 | 40 yr/female | United States | Diabetes | Headache, fever | (+) RT-PCR/PS | 3 | Headache, seizure | (+) Neck stiffness, photophobia | 2 | ME | N/A | Antibiotics, acyclovir, anti-epileptic medication, hydroxychloroquine | Good: The patient's mentation improved and was able to ambulate, eat and use the bathroom, but the hallucinations remained intermittently |
| 7 | 50 yr/male | France | Diabetes, hypertension | Cough, fever, anosmia | (+) RT-PCR/tracheal aspirate | 5 | Status epilepticus | N/A | 5 | E | Right frontal lobe | IVlg | Good: Improved |
| 8 | 50 yr/male | Turkey | N/A | Dyspnea | (+) RT-PCR/PS | N/A | Consciousness disturbance, delirium | N/A | N/A | E | White matter, cortical | Plasmapheresis treatment, LOP/RIT, AZI, CEF | Good: Consciousness was improved |
| 9 | 50 yr/male | Turkey | N/A | Dyspnea | (+) RT-PCR/PS | N/A | Consciousness disturbance, delirium | N/A | N/A | E | White matter, cortical | Plasmapheresis treatment, AZI, HC, FAV | Good: Consciousness was improved |
| #  | Age (yr) | Gender | Location | Comorbidities | Symptoms | Test Results | Neurological Manifestations | Treatment | Outcome |
|----|---------|--------|----------|---------------|----------|--------------|------------------------------|-----------|---------|
| 18 | 26      | 59     | Turkey   | Hypertension, diabetes, obesity | Dyspnea | (+) RT-PCR/PS | N/A | Consciousness disturbance, delirium | N/A | N/A M | N/A Plasmapheresis treatment, AZI, HC, FAV | Dead: Cardiac arrest |
| 19 | 26      | 51     | Turkey   | Hypertension, diabetes | Dyspnea | (+) RT-PCR/PS | N/A | Consciousness disturbance, delirium | N/A | N/A M | N/A Plasmapheresis treatment, AZI, HC, FAV | Good: Consciousness was improved |
| 20 | 26      | 55     | Turkey   | Hypertension | Dyspnea | (+) RT-PCR/PS | N/A | Consciousness disturbance, delirium | N/A | N/A M | N/A Plasmapheresis treatment, AZI, HC, FAV | Poor: Subsequent infection |
| 21 | 26      | 22     | Turkey   | Autism | Dyspnea | (+) RT-PCR/PS | N/A | Consciousness disturbance, delirium | N/A | N/A E | White matter Plasmapheresis treatment, AZI, HC, FAV | Good: Consciousness was improved |
| 22 | 33      | 40     | United States | Obesity, diabetes mellitus | Fever | (+) RT-PCR/NPS | N/A | Syncope | N/A | 1 E | N/A Hydroxychloroquine | Good: Recovery without neurological deficits |
| 23 | 27      | 60     | United Kingdom | N/A | Fever, cough, cognitive fluctuations | (+) RT-PCR/NPS | 5 | Irritability, confusion, asthenia, consciousness (+) Palpomental and glabella reflexes, mutism, (+) moderate nuchal rigidity, severe akinetic syndrome | 1 E | N/A | Lopinavir/ritonavir, hydroxychloroquine, ampicillin, acyclovir | Good: Normal neurological examination and hospital discharged |
| 24 | 28      | 64     | Switzerland | N/A | Weakness, cough, myalgia | (+) RT-PCR/NPS | N/A | Tonic-clonic seizure | 6 E | N/A | Clonazepam, valproate, acyclovir | Good: Improved |
| 25 | 28      | 67     | Switzerland | N/A | Cough | (+) RT-PCR/NPS | N/A | Headache, syncope | Motor perseverations, bilateral grasping, aggressiveness, left hemianopia and sensory hemineglect | 18 E | N/A | Ceftriaxone, amoxicillin, acyclovir | Good: Neurological symptoms resolved, except for a mild headache, hospital discharged |
| 26 | 29      | 8      | South Asian | N/A | Fever, abdominal pain, palmar rash, vomiting | (+) RT-PCR/NPS | N/A | Confused, agitated, headache | (+) Meningeal irritation signs (including nuchal rigidity, Kernig sign and Brudzinski sign), generalized proximal weakness | 1 ME | Corpus callosum IVlg, dexamethasone, anakinra | Poor: Still inpatient, wheelchair bound |
| 27 | 29      | 9      | Caribbean | N/A | Fever, palmar rash, | (+) RT- | N/A | Confused, ataxia, Urinary retention, | 1 E | Corpus callosum | N/A Good: Hospital |
| Age | Sex | Location | Cough, fever | Cerebrospinal fluid | Time between reported viral syndrome and confirmed coronavirus disease-19 (TVC) | Time between reported viral syndrome and onset of neurological symptoms (TVN) | Treatment | Status |
|-----|-----|----------|--------------|---------------------|-------------------------------------------------|-------------------------------------------------|----------------|--------|
| 28  | 30  | 64 yr/male | Fever, cough | (+) RT-PCR/PS | 15 | Lethargic, unresponsive | (+) Meningeal irritation signs (nuchal rigidity, Kernig sign, Brudzinski sign), consciousness alternating between lethargy and irritability, responses to questions were incorrect, (+) ankle clonus, Babinski sign and Chaddock sign | 14 M | N/A | Oxygen inhalation, arbidol, ribavirin, traditional Chinese medicine | Good: Clear consciousness, limb reflexes were relatively active, left lower limb was positive for pathological signs |
| 29  | 31  | 50 yr/female | Cough, fever | (+) RT-PCR/PS | 2 | Altered mental status | N/A | Thalami, temporal lobe, insular lobe | IVlg | N/A | |
| 30  | 18  | 56 yr/male | N/A | N/A | (+) RT-PCR/PS | Consciousness confusion | N/A | N/A | N/A | N/A | Good: Neurological symptoms gradually disappeared |
| 31  | 33  | 65 yr/female | N/A | N/A | (+) RT-PCR/NPS | Reduced consciousness | N/A | N/A | 1 g IVMP 3 d, oral prednisolone taper, levetiracetam, clonazepam | Poor: Incomplete, partial recovery |
| 32  | 33  | 66 yr/female | N/A | N/A | (+) RT-PCR/NPS | Reduced consciousness | N/A | Upper pons, limbic lobes, medial thalami, subcortical cerebral white matter | 1 g IVMP 3 d then oral prednisolone taper, IVlg | Poor: Incomplete, partial recovery |

NA: Not available; M: Male; F: Female; (+): Positive; TVC: Time between reported viral syndrome and confirmed coronavirus disease-19; TVN: Time between reported viral syndrome and onset of neurological symptoms (d); PS: Pharyngeal swab; NPS: Nasopharyngeal swab; E: Encephalitis; M: Meningitis; EM: Encephalomyelitis; RE: Rhombencephalitis; WBCs: White blood cells; CRP: C-reactive protein; LDH: Lactate dehydrogenase; CSF: Cerebrospinal fluid; LOP: Lopinavir; RIT: Ritonavir; AZI: Azitromisin; HC: Hydroxychloroquine; CEF: Ceftriaxone; FAV: Favipiravir; IL-6: Interleukin-6; MRI: Magnetic resonance imaging; AlbQ: Albumin quotient; IVIg: Intravenous immune globulin.

A total of four (12.5%) definite cases of SARS-CoV-2-associated encephalitis/meningitis were those confirmed by positive RT-PCR results in CSF, one (3.13%) was confirmed by positive RT-PCR results in postoperative brain tissue, and one (3.13%) was confirmed by the presence of SARS-CoV-2 antibodies in CSF.

The clinical and laboratory features of the patients with the SARS-CoV-2-associated encephalitis/meningitis are summarized in Tables 3 and 4. Nineteen
| Characteristic | Value (n = 32) |
|---------------|---------------|
| Median age (range), yr | 45.37 (8-75) |
| Male sex, n (%) | 20 (62.5) |
| Female sex, n (%) | 12 (37.5) |
| Time between reported viral syndrome and confirmed COVID-19 (n = 12) | 6 (2-15) |
| General symptoms before the onset of the encephalitis/meningitis, n (%) | 29 (96.67) |
| Fever | 16 (55.17) |
| Cough | 13 (44.83) |
| Diarrhea | 11 (37.93) |
| Myalgia | 4 (13.79) |
| Generalized weakness | 3 (10.34) |
| Headache | 3 (10.34) |
| Vomiting | 3 (10.34) |
| Nasal obstruction | 2 (6.90) |
| Palmar rash | 2 (6.90) |
| Abdominal pain | 1 (3.45) |
| Anosmia | 1 (3.45) |
| Cognitive fluctuations | 1 (3.45) |
| Insomnia | 1 (3.45) |
| Psychological abnormalities | 1 (3.45) |
| Time between reported viral syndrome and onset of neurological symptoms | 7.91 (1-21) |
| Neurological symptoms, n (%) | 32 (100) |
| Consciousness disturbance | 19 (59.38) |
| Seizure | 7 (21.88) |
| Delirium | 6 (18.75) |
| Headache | 6 (18.75) |
| Altered mental status | 3 (9.38) |
| Ataxia | 2 (6.25) |
| Drowsiness | 2 (6.25) |
| Dysphagia | 2 (6.25) |
| Myoclonus | 2 (6.25) |
| Paresthesias | 2 (6.25) |
| Syncope | 2 (6.25) |
| Unsteady gait | 2 (6.25) |
| Autonomic instabilities | 1 (3.13) |
| Diplopia | 1 (3.13) |
| Dizziness | 1 (3.13) |
| Dysarthria | 1 (3.13) |
| Dyskinesias | 1 (3.13) |
| Kinetic tremor | 1 (3.13) |
| Nausea | 1 (3.13) |
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| Symptom                          | n (%)   |
|---------------------------------|---------|
| Oscillopsia                      | 1 (3.13)|
| Paralysis                        | 1 (3.13)|
| Urinary incontinence            | 1 (3.13)|

SARS-CoV-2 infection diagnostic category, n (%)

| Test                               | n (%)       |
|------------------------------------|-------------|
| Nasopharyngeal swab/PT-PCR         | 28 (87.5)   |
| SARS-CoV-2 IgM (Serum)             | 1 (3.13)    |
| SARS-CoV-2 IgG (Serum)             | 1 (3.13)    |
| Tracheal aspirate/PT-PCR           | 1 (3.13)    |
| PCR for SARS-CoV-2 on CSF          | 4 (12.5)    |
| PCR for SARS-CoV-2 in Postoperative brain histopathology | 1 (3.13) |
| SARS-CoV-2 antibody (CSF)          | 3 (9.38)    |

COVID-19: Coronavirus disease-19; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; RT-PCR: Reverse transcriptase-polymerase chain reaction; CSF: Cerebrospinal fluid.

(59.36%) patients were determined to have encephalitis, five (15.63%) were classified as having meningitis, five (15.63%) had meningoencephalitis, two (6.25%) had encephalomyelitis, and one (3.13%) had rhombencephalitis and myelitis. As shown by neuroimaging, the encephalitis/meningitis caused by SARS-CoV-2 mainly damaged the temporal lobe (n = 5, 15.63%), frontal lobe (n = 3, 9.38%), corpus callosum (n = 3, 9.38%), white matter (n = 3, 12.5%), cervical spinal cord (n = 3, 12.5%), thalami (n = 2, 9.38%), and cortex (n = 2, 6.25%).

In this group of SARS-CoV-2-associated encephalitis/meningitis patients, only 22 had chest radiogram performed, and of these, 81.82% (18/22) had positive findings. Surprisingly, 18.18% (4/22) of patients’ chest radiograms were negative. Twenty-one (65.63%) patients underwent blood test analysis. Six (28.57%) patients had a low/normal white blood cell (WBC) count, ten (47.62%) had a high WBC count, four (19.05%) had lymphopenia, 14 (66.67%) had high C-reactive protein (CRP), ten (57.14%) had high D-dimer, and eight (38.1%) had high ferritin. Thirty-one (96.88%) patients underwent CSF analysis. Thirteen (13/22, 59.09%) patients with CSF data had an increased protein level, nine (9/23, 39.13%) had an increased WBC level, and two (2/5, 40%) had increased intracranial pressure. One patient had a positive anti-NMDA antibody in CSF (Tables 3 and 4).

In this group of SARS-CoV-2-associated encephalitis/meningitis patients, 31 (96.88%) had neuroimaging performed, and of these 61.29% (18/31) had abnormal findings of brain damage. Approximately 38.71% (11/31) of patients had no significant findings. Among these ten patients, eight (80%) had EEGs that showed a diffuse slow wave, and two (20%) had EEGs that showed a focal epileptic wave. These EEG findings suggest that CNS injury may be related to SARS-CoV-2 infection in these patients.

Twenty-eight (87.5%) patients were administered with specific treatment, of whom 22 (78.57%) received antibiotics, 14 (50%) received antiretroviral drugs, seven (25%) received corticoids, six (21.43%) received plasmapheresis treatment, six (21.43%) received intravenous immunoglobulin (IVlg), six (21.43%) received anticonvulsant medications, and one each received surgery, interleukin-1 receptor antagonist, and traditional Chinese medicine. Twenty-nine (90.63%) of patients had recorded outcomes; the prognosis was good in 21 (65.63%) patients and poor in five (15.64%), and three (9.38%) patients died (Tables 1 and 4).

**DISCUSSION**

SARS-CoV-2 involves multiple organs including the central and peripheral nervous system[15]. In a series of studies in Wuhan, 78 of 214 COVID-19 patients, recruited over 4 wk, developed neurological manifestations. These patients tended to be more severely affected, older, and with more complications, and for some, the neurological...
Table 3 Auxiliary examination of acute neurologic illness among patients with confirmed encephalitis/meningitis with evidence of severe acute respiratory syndrome coronavirus 2 infection

| No. | Ref. | Chest radiogram | Blood test | CSF finding | SARS-CoV-2 in CNS | Neuroimaging | EEG |
|-----|------|----------------|------------|-------------|-------------------|--------------|-----|
| 1   | 16   | CT showed multiple subpleural ground glass opacities | Low WBC count (3.3 × 10⁹ /L) and lymphopenia (0.8 × 10⁹ /L) | WBCI cell/mm³, protein 0.27 g/L, ADA 0.17 U/L and sugar 3.14 mmol/L; the evidence of bacterial or tuberculous infection (-) | Anti-SARS-CoV-2 IgM/IgG in CSF (-) | Skull CT was normal | N/A |
| 2   | 9    | CT showed that there was small ground glass opacity on the right superior lobe and both sides of the inferior lobe | High WBC, neutrophil dominant, relatively low lymphocytes; high CRP | Pressure was greater than 320 mmH₂O, cell count 12 cells/mm³, mononuclear 10 cells/mm³ and polymorphonuclear 2 cells/mm³. Anti-HSV 1 and varicella-zoster IgM antibodies (-) | SARS-CoV-2 RNA in CSF (-) | MRI showed hyperintensity along the wall of right lateral ventricle and hyperintense signal changes in the right mesial temporal lobe and hippocampus | N/A |
| 3   | 2    | CT showed patchy bilateral consolidations | WBC 10.49 × 10⁹ /L, Neut 6.63 × 10⁹ /L, Lym 2.86 × 10⁹ /L; CRP 55 mg/L | WBC 1060 cells/mm³, glucose 70 mg/dL, proteins 65.4 mg/dL; HSV/EBV/CMV/VZV-DNA (-); enterovirus (-); Ab anti-Ca++Channel/AMPA1,2/CASPR 2/LGI1 (-); Ab anti-NMDAR (+) | SARS-CoV-2 RNA in CSF (-) | Neuroradiology did not show significant findings | The EEG showed theta activity at 6 Hz, unstable, non-reactive to visual stimuli. No significant asymmetries were seen |
| 4   | 17   | N/A | N/A | N/A | SARS-CoV-2 RNA in Postoperative brain histopathology (+) | MRI showed hyperintense signal in the left temporal lobe in T2 and T2 FLAIR imaging | N/A |
| 5   | 36   | CT showed multifocal brain lesions | High WBC count 12.9 × 10⁹ /L, high procalcitonin 0.10 ng/mL, high D-dimer 0.790 mg/L | SARS-CoV-2 RNA PCR in CSF (+) | A right frontal intracerebral hematoma associated with subarachnoid hemorrage in the ipsilateral sylvian fissure and frontal and temporal lobes; a thin, acute subdural hematoma was also evident. The hematoma appeared surrounded by edema and caused midline shift. Bilateral supratentorial leptomeningeal increased enhancement was detected | N/A |
| 6   | 20   | CT showed ground glass opacities in the bilateral inferior lobes | WBC count 5.96 × 10⁹ /L, lymphocytopenia 1.1 × 10⁹ /L, PLT 143 × 10⁹ /L; CRP 55.3 mg/L | Pressure 30 cmH₂O, nucleated 115 cells/mm³, protein > 2 g/L; nucleated cell count remained strongly increased even after correction for the traumatic tap (approximately 1 nucleated cell/700 erythrocytes) | Markedly increased levels of IgM for SARS-CoV-2 S1 and E proteins in CSF, SARS-CoV-2 RNA in CSF (-) | MRI showed non-enhancing cerebral edema and diffusion weighted imaging abnormalities predominantly involving the right cerebral hemisphere, as well as brain herniation. An occlusive thrombus was identified in the right internal carotid artery, and edema was also identified in the cervical spinal cord | N/A |
| 7   | 20   | CT showed right lower lobe infiltrate | Pressure 30 cmH₂O, nucleated 115 cells/mm³, erythrocytes 7574 cells/mm³, protein > 2 g/L; nucleated cell count remained strongly increased even after correction for the traumatic tap (approximately 1 nucleated cell/700 erythrocytes) | Markedly increased levels of IgM for SARS-CoV-2 S1 and E proteins in CSF, SARS-CoV-2 RNA in CSF (-) | MRI showed non-enhancing cerebral edema and diffusion weighted imaging abnormalities predominantly involving the right cerebral hemisphere, as well as brain herniation. An occlusive thrombus was identified in the right internal carotid artery, and edema was also identified in the cervical spinal cord | N/A |
| 8   | 20   | CT showed bilateral diffuse ground glass infiltrates | Pressure 48 cmH₂O, no pleocytosis, erythrocytes 27 cells/mm³, a mildly increased protein level | Markedly increased levels of IgM for SARS-CoV-2 S1, SARS-CoV-2 RNA in CSF (-) | MRI showed a non-enhancing hyperintense lesion within the splenium of the corpus callosum on fluid-attenuated inversion recovery and diffusion weighted imaging sequences | EEG showed diffuse slowing with a suggestion that the myoclonus was seizure-related | N/A |
| 9   | 20   | CT showed multifocal | Normal opening pressure; levels of Arteries remained normal | Markedly increased | MRI showed an equivocal non-enhancing area of fluid- | N/A |
| Case | Symptoms | Test Results | Diagnosis |
|------|----------|--------------|-----------|
| 10   | N/A      | N/A          | CT was negative |
| 11   | CT showed multiple peripheral patchy ground-glass opacities | ANA = 2.7, positive; WBC 20 × 10⁹/L, Neut 15 × 10⁹/L, LYM 0.8 × 10⁹/L, PLT 168 × 10⁹/L, CRP 480 mg/L | MRI revealed T2-FLAIR high signal intensities in bilateral thalami, medial temporal and pons. Corresponding areas in T1 images were hypo-signal |
| 12   | CT was normal | Blood cell counts, transaminases, bilirubin, CPK, coagulogram, electrolytes, renal function, and CRP were all normal | Brain MRI was normal; cervical spinal cord MRI showed a small left lateral ventral lesion with T2/STIR hypersignal, measuring about 0.4 cm in its sagittal plane |
| 13   | X-ray showed a right lower zone consolidation | WBC 7.0 × 10⁹/L, lymphocytes 1.2 × 10⁹/L, high CRP 50 mg/L, high ALT 88 U/L | MRI of the brain and cervical spine suggested an inflammatory rhomboencephalitis/myelitis, the increased signal lesion in the right interior cerebellar peduncle, extending to a small portion of the upper cord. The lesion measured 13 mm in maximum cross-sectional area and 28 mm in longitudinal extent. There was swelling at the affected tissue and associated micro-haemorrhage |
| 14   | X-ray and CT were normal | WBC 7.1 × 10⁹/L, white cells 70 cells/mm³ with 100% lymphocytes, protein 0.1 g/L, glucose 120 mg/dL | CT of the head without contrast was normal |
| 15   | N/A      | Leukocyte 1 cell/mm³, protein 0.66 g/L, glucose 10.5 mmol/L | EEG showed generalized slowing with no epileptic discharges |
| 16   | CT showed multiple subpleural ground glass opacities | WBC 26.53 × 10⁹/L, PLT 202 × 10⁹/L, CRP 135 mg/L, D-dimer 6.27 mg/L, LDH 560 IU/L, IL-6 481 pg/mL, ferritin 1763 ng/mL | MRI findings showing cortical or white matter hyperintensities, contrast enhancement, and sulcal hemorrhagic features, all of which are considered compatible with meningoencephalitis |
| 17   | CT showed multiple subpleural ground glass opacities | WBC 20.21 × 10⁹/L, PLT 540 × 10⁹/L, CRP 82.9 mg/L, D-dimer 6.6 mg/L, LDH 304 IU/L, IL-6 - pg/mL, ferritin 2918 ng/mL | MRI findings showing cortical or white matter hyperintensities, contrast enhancement, and sulcal hemorrhagic features |
| 18   | CT showed multiple | WBC 17.081 × 10⁹/L, PLT protein 0.657 g/L, glucose 121 mg/dL | MRI was normal |

**Note:** The table provides a summary of various cases with symptoms, test results, and diagnoses related to SARS-CoV-2-associated encephalitis and meningitis.
| Patient | Date | Findings | Abnormalities | Microbiological Tests | Imaging | Laboratory Tests | Clinical Findings |
|---------|------|----------|---------------|----------------------|---------|-----------------|------------------|
| 19      | 26   | CT showed multiple subpleural ground glass opacities | WBC 11.49 × 10^9/L, PLT 660 × 10^9/L, CRP 142.2 mg/L, D-dimer 0.91 mg/L, LDH 271 IU/L, IL-6 78 pg/mL, ferritin 896 ng/mL | Protein 0.131 g/L, glucose 120 mg/dL, cell count 0, CSF IgG 3.25 mg/L, IgG index 0.780, AlbQ 5.14, oligoclonal band none | MRI was normal | N/A |
| 20      | 26   | CT showed multiple subpleural ground glass opacities | WBC 42.70 × 10^9/L, PLT 299 × 10^9/L, CRP 732.3 mg/L, D-dimer 6.97 mg/L, LDH 709 IU/L, IL-6 510 pg/mL, ferritin 5235 ng/mL | Protein 0.52 g/L, glucose 67 mg/dL, cell count 0, CSF IgG 6.66 mg/L, IgG index 0.380, AlbQ 14.1, oligoclonal band none | MRI was normal | N/A |
| 21      | 26   | CT showed multiple subpleural ground glass opacities | WBC 17.83 × 10^9/L, PLT 664 × 10^9/L, CRP 431.8 mg/L, D-dimer 7.93 mg/L, LDH 1110 IU/L, IL-6 9192 pg/mL, ferritin 555 ng/mL | Protein 0.57 g/L, glucose 59 mg/dL, cell count 0, CSF IgG 5.71 mg/L, IgG index 0.520, AlbQ 10.0, oligoclonal band none | MRI findings showing cortical or white matter hyperintensities, contrast enhancement, and sulcal hemorrhagic features | N/A |
| 22      | 33   | X-ray and CT were normal | N/A | Bacterial culture and herpes simplex virus type 1 (−) | SARS-CoV-2 RNA in CSF (−) | N/A |
| 23      | 27   | X-ray showed moderate bilateral interstitial pneumonia | High D-dimer 0.968 mg/L | Lymphocytic pleocytosis 18 cells/mm³, protein 69.6 mg/dL, oligoclonal bands (−) | SARS-CoV-2 RNA in CSF (−) | MRI with gadolinium contrast did not reveal any significant alterations or contrast-enhanced areas | EEG exhibited generalized slowing, with decreased reactivity to acoustic stimuli |
| 24      | 28   | N/A | N/A | Protein 0.466 g/L, glucose 59 mg/dL, cell count 17 cells/mm³, lymphocyte 97%: anti-NMDA antibodies(−) | SARS-CoV-2 RNA in CSF (−) | MRI was normal | EEG revealed nonconvulsive, focal status epilepticus (abundant bursts of anterior low-medium voltage irregular spike-and-waves superimposed on an irregularly slowed theta background); a follow-up EEG 24 h after admission showed a moderate theta background slowing, without epileptiform features |
| 25      | 28   | N/A | N/A | High lymphocytic pleocytosis, iral/bacterial pathogens (−) | SARS-CoV-2 RNA in CSF (−) | MRI was normal | N/A |
| 26      | 29   | N/A | CRP 44.8 mg/L, ferritin 1414 mg/mL, D-dimer 0.625 mg/L, LDH 1016 U/L | WBC count 8 cells/mm³, protein 0.2 g/L, oligoclonal band test (−) | SARS-CoV-2 RNA in CSF (−) | CT showed hypodensity of the splenium of the corpus callosum | EEG showed mild diffuse slowing |
| 27      | 29   | N/A | CRP 31.3 mg/L, ferritin 1192 mg/mL, D-dimer 0.694 mg/L, LDH 980 U/L | WBC count 2 cells/mm³, protein 0.19 g/L, oligoclonal band test (−) | SARS-CoV-2 RNA in CSF (−) | Axial T2 of MRI showed signal changes of the genu and corpus callosum (top) and bilateral centrum semiovale with restricted diffusion (bottom) | EEG showed diffuse slow activity |
| 28      | 30   | CT showed multiple ground-glass opacities | WBC 3.3 × 10^9/L, lymphocyte 24.4% | Pressure 200 cm H₂O, cell count 1 cell/mm³, protein 0.275 g/L, glucose 3.14 | SARS-CoV-2 RNA in CSF (−) | CT did not reveal significant abnormalities | N/A |
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| Case | CT Findings | Bacterial/HSV Type 1 and 2 or Varicella Zoster Virus/West Nile Virus | CSF Findings | MRI Findings |
|------|-------------|-------------------------------------------------------------------|--------------|--------------|
| 29   | N/A         | Bacteria/HSV type 1 and 2 or varicella zoster virus/West Nile virus | N/A          | MRI showed acute necrotizing encephalitis were seen in the bilateral thalami, medial temporal lobes, and sub-insular regions |
| 30   | N/A         | SARS-CoV-2 RNA in CSF +                                             | CT was normal | MRI brain normal |
| 31   | N/A         | CSF matched oligoclonal band                                       | SARS-CoV-2 RNA in CSF - | MRI brain: T2 hyperintense signal changes in upper pons, limbic lobes, medial thalami and subcortical cerebral white matter |
| 32   | N/A         | CSF protein raised, oligoclonal band test -                       | SARS-CoV-2 RNA in CSF - | MRI brain: T2 hyperintense signal changes in upper pons, limbic lobes, medial thalami and subcortical cerebral white matter |

NA: Not available; CT: Computed tomography; EEG: Electroencephalography; CSF: Cerebrospinal fluid; MRI: Magnetic resonance imaging; FLAIR: Fluid-attenuated inversion recovery; WBC: White blood cell; N: Neutrophils; L: Lymphocyte; PLT: Platelet; CRP: C-reactive protein; GGT: Gamma glutamyl transferase; ALT: Alanine aminotransferase; SCC: Splenium of corpus callosum.

Symptom was the first presentation of COVID-19. The widespread effects of COVID-19 include neurological disorders, but there have been no detailed clinical reports of their nature to date. Neurological complications caused by SARS-CoV-2 are similar to those caused by other coronaviruses, especially severe acute respiratory syndrome (SARS) in 2003 and Middle East acute respiratory syndrome in 2012. Cases described in those reports include encephalopathy, encephalitis, stroke, hemorrhage, acute disseminated encephalomyelitis, and Guillain-Barré syndrome. About 80% of COVID-19 patients have no or only mild symptoms, especially in children and young adults. Up to 20% of patients with SARS-CoV-2 infection will develop some degrees of severe symptoms. Severe patients were more likely to have neurological complications such as encephalitis, meningitis, stroke, and encephalopathy than non-severe patients. Most patients with SARS-CoV-2 infection were severe or critically ill, and they required ICU treatment and mechanical ventilation. Lung abnormalities were found in almost all patients with SARS-CoV-2-associated encephalitis. Therefore, early diagnosis of viral encephalitis is essential to improve the prognosis of COVID-19 patients.

In this study, we systematically reviewed the clinical data of SARS-CoV-2-associated encephalitis/meningitis that were identified in the context of the COVID-19 global pandemic. To our knowledge, this is the first largest comprehensive retrospective review of any published studies, including case or case series, that have been conducted to assess the role of SARS-CoV-2 infection in patients diagnosed with encephalitis/meningitis during the SARS-CoV-2 outbreak. We systematically described the epidemiological, clinical, radiological, laboratory, therapeutic, and prognostic outcomes. This latest review focuses on clinical characteristics that may help clinicians identify potential patients early and begin timely and appropriate...
Table 4 Auxiliary examination of the 32 coronavirus disease-19 patients with encephalitis/meningitis

| Characteristic                                                                 | Value (n = 32)          |
|--------------------------------------------------------------------------------|-------------------------|
| Subtype, n (%)                                                                 |                         |
| Encephalitis                                                                   | 19 (59.36)              |
| Meningitis                                                                     | 5 (15.63)               |
| Meningoencephalitis                                                            | 5 (15.63)               |
| Encephalomyelitis                                                              | 2 (6.25)                |
| Rhombencephalitis                                                              | 1 (3.13)                |
| Myelitis                                                                       | 1 (3.13)                |
| Primary target identified by neuroimaging, n (%)                              |                         |
| Temporal lobe                                                                  | 5 (15.63)               |
| White matter                                                                   | 4 (12.5)                |
| Corpus callosum                                                                | 3 (9.38)                |
| Frontal lobe                                                                   | 3 (9.38)                |
| Cervical spinal cord                                                           | 3 (9.38)                |
| Thalami                                                                        | 3 (9.38)                |
| Cortical                                                                       | 2 (6.25)                |
| Limbic lobe                                                                    | 1 (3.13)                |
| Brain stem                                                                     | 1 (3.13)                |
| Upper pons                                                                      | 1 (3.13)                |
| Hippocampus                                                                    | 1 (3.13)                |
| Insular lobe                                                                   | 1 (3.13)                |
| Lateral ventricle                                                              | 1 (3.13)                |
| Leptomeningeal                                                                 | 1 (3.13)                |
| Pontine                                                                        | 1 (3.13)                |
| Right cerebral hemisphere                                                      | 1 (3.13)                |
| Supratentorial                                                                 | 1 (3.13)                |
| Chest radiogram, n (%)                                                         |                         |
| Negative/total                                                                 | 4/22 (18.18)            |
| Positive/total                                                                 | 18/22 (81.82)           |
| Not available/total                                                            | 8/30 (26.67)            |
| Blood test, n (%)                                                              |                         |
| WBC count (low/normal)                                                         | 6/21 (28.57)            |
| WBC count (high)                                                               | 10/21 (47.62)           |
| Lymphopenia (low)                                                              | 4/21 (19.05)            |
| CRP (high)                                                                     | 14/21 (66.67)           |
| D-dimer (high)                                                                 | 12/21 (57.14)           |
| Ferritin (high)                                                                | 8/21 (38.1)             |
| IL-6 (high)                                                                    | 1/21 (4.76)             |
| procalcitonin (high)                                                           | 1/21 (4.76)             |
| ANA (positive)                                                                 | 1/21 (4.76)             |
| N/A                                                                            | 11 (3.13)               |
| Results of CSF analysis, n (%)                                                 |                         |
Encephalitis/meningitis is the neurological complication in patients with SARS-CoV-2 infection. During the ongoing pneumonia epidemic, a few isolated case reports of SARS-CoV-2 associated encephalitis/meningitis, has been detected in patients undergoing sequencing, thus clinically confirming SARS-CoV-2 viral encephalitis. This provides a solid foundation for coronavirus encephalitis. Transcribral spread of SARS-CoV-2 to the brain is also supported by the fact that hyposmia anosmia is one of the earliest symptoms with which patients usually present. Anosmia and abnormal brain function can help distinguish it from other encephalopathy.

Currently, most of the patients with SARS-CoV-2 infection and neurological complications are elderly people, and most of them are more than 50 years old. This
age group is more likely to have complications and develop into severe disease\(^{[40,41]}\). In our review, however, COVID-19 patients with encephalitis or meningitis can be found in all age groups, and the main age group is over 30 years old (68.75%). The incidence of SARS-CoV-2-associated encephalitis or meningitis is relatively low in children and adolescents (31.25%), which may be related to the relatively mild illness of COVID-19 in children and adolescents. The cases were determined as SARS-CoV-2-associated encephalitis or meningitis according to WHO criteria (SARS-CoV-2 RNA PCR positive results from nasopharyngeal swab, CSF, or pathological specimen)\(^{[42]}\).

Encephalitis is an infection or inflammation that involves the brain and surrounding tissues. Meningitis is an infection or inflammation that affects the meninges and spinal cord\(^{[43]}\). SARS-CoV-2-associated encephalitis/meningitis is always preceded by commoner clinical features about 1 wk ago (7.91 d, range 1-21 d), like fever (55.17%), cough (44.83%), dyspnea (37.93%), and diarrhea (13.79%). Most COVID-19 patients who develop encephalitis/meningitis complications are referred to ICU for hospitalization\(^{[44]}\). Symptoms of viral meningitis typically include fever, neck pain, photophobia, and/or photophobia. Symptoms of viral encephalitis may include abnormal brain function (altered mental state, personality change, and behavioral or verbal abnormalities), movement disorders, and focal neurological signs, like hemiplegia, facioplegia, or abnormal sensation. Seizures may occur in both viral meningitis and encephalitis\(^{[45]}\). Like other viruses, the main clinical symptoms of SARS-CoV-2-associated encephalitis/meningitis are consciousness disturbance (59.38%), seizure (21.88%), delirium (18.75%), and headache (18.75%). Laboratory indicators of COVID-19 showed lymphocytosis, elevated D-dimer, and altered ground glass opacity on chest imaging\(^{[46]}\). Among inflammatory markers in patients with SARS-CoV-2-associated encephalitis/meningitis, high CRP (66.67%) and D-dimer (57.14%), and raised ferritin (38.1%) were reported in many cases.

To date, virus-induced immune response leading to inflammatory damage of the CNS and direct invasion are the two main pathophysiological mechanisms of SARS-CoV-2-associated encephalitis\(^{[47,48]}\). SARS-CoV-2 enters cells by binding to ACE-2 receptors. The ACE-2 receptor is expressed not only in the lungs but also in the CNS\(^{[49,50]}\). The combination of SARS-CoV-2 and ACE2 receptor may lead to increased secretion of inflammatory factors such as TNF-alpha, IL-1, and IL-6, which may be the cause of neuropsychiatric symptoms\(^{[51]}\). In the absence of evidence of direct viral invasion, SARS-CoV-2-associated encephalitis may be associated with immune-mediated inflammatory mechanisms (patient 3)\(^{[15]}\). Although the human respiratory system is the target organ of human coronavirus, SARS-CoV-2 also has the ability to directly invade the nervous system\(^{[40]}\). It has been demonstrated in rodent models that SARS-CoV-2 invades the CNS and causes neuronal death\(^{[49]}\). Based on the known neurotropism of previous SARS-CoV strains, SARS-CoV-2 also can spread to the CNS directly, which could access the CNS via olfactory pathways or the bloodstream, causing meningitis and encephalitis\(^{[52,53]}\).

By definition, SARS-CoV-2-associated encephalitis/meningitis is an inflammatory process, and supporting evidence includes the presence of COVID-19 patients with CSF pleocytosis and elevated protein\(^{[54]}\). Definitive evidence about direct neuroinvasiveness of SARS-CoV-2 would include SARS-CoV-2 RNA PCR positive tests in CSF, SARS-CoV-2-specific antibodies positive tests in CSF, or SARS-CoV-2 RNA or antigen positive tests in brain tissue obtained at autopsy or biopsy\(^{[55]}\). Although more and more cases of SARS-associated encephalitis have been reported, few (25%) actually meet the strict criteria for direct SARS-CoV-2-associated encephalitis. In the majority of reported patients with COVID-19-associated encephalopathy, CSF was reported as normal (Table 1). Thus, detailed nervous system physical examination, auxiliary examination, and positive rate of SARS-CoV-2 detection in CSF are very important to provide direct neurotropic evidence of SARS-CoV-2\(^{[49]}\).

In SARS-CoV-2-associated encephalitis, infection or inflammation can involve any part of the brain, especially the temporal lobe (15.63%), white matter (12.5%), frontal lobe (9.38%), and corpus callosum (9.38%). Neuroimaging abnormalities, in SARS-CoV-2-associated encephalitis, usually present with high T2/FLAIR signal hyperintensity in the subcortical white matter or other parts of brain injury. There are also many COVID-19 patients (38.71%) who do not have significant neuroimaging changes in encephalitis\(^{[56,57]}\).

In the majority of patients (8/10, 80%) with SARS-CoV-2-associated encephalitis, the EEG manifestation was diffuse slow waves, and some patients present with a focal epileptic wave or generalized delta activity. Slow speed and theta activity in EEGs of COVID-19 patients are not necessarily direct evidence of encephalitis and may be related to depressants, drowsiness, muzziness, hypoxia, and other CNS depressive
However, it is important to note that when EEGs show monomorphic biphasic high amplitude delta waves associated with occasional myoclonic muscular activity, this may suggest that brain damage is associated with the direct effect of COVID-19 itself\(^5\).

Patients with encephalitis generally need ICU care and occasionally mechanical ventilation. More than 50% of patients with SARS-CoV-2-associated encephalitis/meningitis were treated with antibiotics and antiviral drugs (especially hydroxychloroquine, 42.86%). Some patients were also treated with IVIg and corticoids. Anticonvulsant medications were used in the patients with seizure. Dogan et al\(^26\) reported plasma exchange in a series of six patients with SARS-CoV-2-associated autoimmune meningoencephalitis.

In general, the presence of neurological disease in COVID-19 patients is associated with higher mortality, disturbance of consciousness, refractory epilepsy, and severe physical disability. However, we reviewed published case reports and found that most COVID-19 patients with encephalitis or meningitis (21/32, 65.63%) improved after systematic treatment. Three patients died and other patients remained in ICU.

## CONCLUSION

In summary, given the high neurotropism potential of SARS-CoV-2, the lack of reports of COVID-19 patients complicated with encephalitis or meningitis is surprising\(^58\). Encephalitis/meningoencephalitis may cause direct damage to the brainstem respiratory center, which may be one of the reasons for the extremely high fatality rate in patients with COVID-19. Detailed biopsy or autopsy neuropathology studies should answer this question\(^59\). From the perspective of infectious diseases of the CNS, the cases of SARS-CoV-2-associated encephalitis that were reported lack direct evidence of SARS invading the nervous system, while the cases of COVID-19 patients who were tested for CSF while excluding other potential diagnoses were only accidental reports. Therefore, we should conduct appropriate investigations to exclude other identified brain infections and parainfluenza before attributing a condition to SARS CoV-2\(^60\). The appropriate use of definitions and exclusion of potential similar diseases are important to reduce over-diagnosis of SARS-CoV-2-associated encephalitis or meningitis.

## ARTICLE HIGHLIGHTS

### Research background
Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has quickly spread around the world and become a global health emergency. There were over 47690000 confirmed coronavirus disease-19 (COVID-19) cases and 1210000 reported deaths in 216 countries worldwide.

### Research motivation
SARS-CoV-2 may cause severe neurological complications, such as encephalopathy and encephalitis. However, it has not been established if there are specific clinical characteristics of encephalitis/meningitis after SARS-CoV-2.

### Research objectives
The objective of this study was to identify specific clinical features of cases of encephalitis/meningitis associated with SARS-CoV-2 infection in the context of this virus pandemic and investigate their relationship with SARS-CoV-2 infection.

### Research methods
We conducted a search of the medical literature using MEDLINE (accessed from PubMed) and Google Scholar from December 1, 2019 to September 13, 2020 through terms “COVID-19 and encephalitis, meningitis” and “SARS-CoV-2 and encephalitis, meningitis”. Then we analyzed clinical features of COVID-19 patients complicated with encephalitis/meningitis in these articles.

### Research results
We identified 22 articles that included a total of 32 encephalitis/meningitis patients...
with confirmed SARS-CoV-2 infection. Approximately 68.75% had symptoms of SARS-CoV-2 infection in about 1 wk preceding the onset of neurological symptoms. The most common neurological symptoms were consciousness disturbance, seizure, delirium, and headache. The mainly damaged targets identified by neuroimaging included the temporal lobe, white matter, frontal lobe, corpus callosum, and cervical spinal cord (9.38%). Eighty percent of patients had EEGs that showed a diffuse slow wave, and 65.63% of patients improved following systemic therapy.

**Research conclusions**

Encephalitis/meningitis is the common neurological complication in patients with COVID-19. From the perspective of infectious diseases of the central nervous system, the cases of SARS-CoV-2-associated encephalitis that were reported lack direct evidence of SARS invading the nervous system, while the cases of COVID-19 patients who were tested for cerebrospinal fluid while excluding other potential diagnoses were only accidental reports. The appropriate use of definitions and exclusion of potential similar diseases are important to reduce over-diagnosis of SARS-CoV-2-associated encephalitis or meningitis.

**Research perspectives**

We should conduct appropriate investigations to exclude other identified brain infections and parainfluenza before attributing a condition to SARS-CoV-2. The appropriate use of definitions and exclusion of potential similar diseases are important to reduce over-diagnosis of SARS-CoV-2-associated encephalitis or meningitis.

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