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SYSTEMATIC REVIEWS

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

Liang Huo, Kai-Li Xu, Hua Wang

ORCID number: Liang Huo 0000-0002-6711-2950; Kai-Li Xu 0000-0001-6148-5628; Hua Wang 0000-0001-8701-0129.

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Liang Huo, Department of Pediatrics, Shengjing Hospital of China Medical University, Shenyang 110004, Liaoning Province, China

Kai-Li Xu, Department of Pediatric Neurology, Children's Hospital Affiliated to Zhengzhou University, Zhengzhou 450018, Henan Province, China

Kai-Li Xu, Department of Pediatric Neurology, Henan Children's Hospital, Zhengzhou 450018, Henan Province, China

Hua Wang, Department of Pediatric Neurology, Shengjing Hospital of China Medical University, Shenyang 110004, Liaoning Province, China

Corresponding author: Liang Huo, MD, PhD, Associated Professor, Department of Pediatrics, Shengjing Hospital of China Medical University, No. 36 Sanhao Street, Heping District, Shenyang 110004, Liaoning Province, China. huol@sj-hospital.org

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

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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

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-relatedencephalitis/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, hypogeusia, or dysgeusia[6,7].

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 neurological deficits, and consciousness disorders[8]. 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*[9] 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[11]. 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[12-14].

The sensitivity of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) of SARS-CoV-2 to detect acute COVID-19 in appropriately treated naso-pharyngeal swabs is high, but current data are limited to evaluate the sensitivity of this technique in CSF in patients with neurological disease[15]. 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[16].

Since the SARS-CoV-2 epidemic, numerous studies have been published on SARS-CoV-2-related encephalitis/meningitis[11,16-18], 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[2,9,16-38].

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

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

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) and extensor plantar response	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	Right lateral ventricle, mesial temporal lobe, hippocampus	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, IVIg	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	Sulbactam/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	Right cerebral hemisphere, cervical spinal cord	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

								stimuli					
9	20	64 yr/male	United States	Hypertension	Cough, dyspnea, fever	(+) RT-PCR/NPS	N/A	Myoclonus	Absent oculocephalic reflex and withdrawal to pain, diminished deep tendon reflexes	N/A	E	Right temporal lobe	Hydroxychloroquine	Good: Hospital discharged without major neurologic sequelae
10	21	11 yr/male	United States	N/A	Generalized weakness, fever	(+) RT-PCR/PS	3	Status epilepticus	N/A	3	E	Frontal lobe	Anticonvulsant medications	Good: Recovery
11	22	39 yr/female	Iran	N/A	Fever, myalgia, dry cough	(+) Anti-SARS- CoV-2-IgM, IgG in serum	10	Drowsiness, decline unconsciousness, seizure, headaches	N/A	10	E	Temporal lobe, pontine, thalami	Broad-spectrum IV antibiotics, hydroxychloroquine, atazanavir, IVIg, levetiracetam, methylprednisolone	Good: Normal consciousness, no diplopia or other abnormal findings
12	37	42 yr/female	Brazil	N/A	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	EM	Cervical spinal cord	Corticosteroids	Good: Recovery
13	23	40 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, hiccups and dribbling when eating or drinking	Facial weakness, reduced tongue movements, limb ataxia	13	RE, myelitis	Brain stem; cervical spine	Gabapentin	Good: Neurological symptoms improved steadily and hospital discharged
14	24	41 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
15	25	69 yr/male	France	Diabetes, hypertension	Cough, fever, anosmia	(+) RT-PCR/tracheal aspirate	5	Status epilepticus	N/A	5	E	Right frontal lobe	IVIg	Good: Improved
16	26	49 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
17	26	59 yr/male	Turkey	Hypertension	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

18	26	59 yr/male	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 yr/female	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 yr/male	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 yr/male	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 yr/female	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 yr/male	United Kingdom	N/A	Fever, cough, cognitive fluctuations	(+) RT-PCR/NPS	5	Irritability, confusion, asthenia, consciousness	(+) Palmomental 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 yr/female	Switzerland	N/A	Weakness, cough, myalgia	(+) RT-PCR/NPS	N/A	Tonico-clonic seizure	Disoriented, attention deficit, bilateral grasping, psychotic symptoms (hyper-religiosity with mystic delusions, visual hallucinations), averbal and motor perseverations	6	E	N/A	Clonazepam, valproate, acyclovir	Good: Improved
25	28	67 yr/female	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 yr/male	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	IVIg, dexamethasone, anakinra	Poor: Still inpatient, wheelchair bound
27	29	9 yr/male	Caribbean	N/A	Fever, palmar rash,	(+) RT-	N/A	Confused, ataxia,	Urinary retention,	1	E	Corpus callosum	N/A	Good: Hospital

					vomiting	PCR/NPS		dysarthria, headache	bilateral proximal leg weakness					discharged
28	30	64 yr/male	China	Health	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	United States	N/A	Cough, fever	(+) RT-PCR/PS	2	Altered mental status	N/A	2	E	Thalami, temporal lobe, insular lobe	IVIg	N/A
30	18	56 yr/male	China	N/A	N/A	(+) RT-PCR/PS	N/A	Consciousness confusion	N/A	N/A	M	N/A	N/A	Good: Neurological symptoms gradually disappeared
31	33	65 yr/female	United Kingdom	N/A	N/A	(+) RT-PCR/NPS	N/A	Reducedconsciousness	N/A	N/A	E	N/A	1 g IVMP 3 d, oral prednisolone taper, levetiracetam, clonazepam	Poor: Incomplete, partial recovery
32	33	66 yr/female	United Kingdom	N/A	N/A	(+) RT-PCR/NPS	N/A	Reducedconsciousness	N/A	N/A	E	Upper pons, limbic lobes, medial thalami, subcortical cerebral white matter	1 g IVMP 3 d then oral prednisolone taper, IVIg	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; ME: Meningoencephalitis; 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: Faviripavir; IL-6: Interleukin-6; MRI: Magnetic resonance imaging; AlbQ: Albumin quotient; IVIg: Intravenous immune globulin.

mental status (n = 3, 9.38%). 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[2,9,16-31,33,37-38]. Nineteen

Table 2 Clinical and demographic characteristics of the 32 coronavirus disease-19 patients with encephalitis/meningitis

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)
Dyspnea	11 (37.93)
Diarrhea	4 (13.79)
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)

Oscillopsia	1 (3.13)
Paralysis	1 (3.13)
Urinary incontinence	1 (3.13)
SARS-CoV-2 infection diagnostic category, *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. Ten (31.25%) patients received EEG to assess unexplained consciousness disturbance, myoclonus, seizure, headache, altered mental status, dysarthria, and responsiveness. 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 (IVIg), 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 (3.3×10^9/L) and lymphopenia (0.8×10^9/L)	WBC1 cell/mm^3, 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 mmH_2O, cell count 12 cells/mm^3, mononuclear 10 cells/mm^3 and polymorphonuclear 2 cells/mm^3. 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 temporallobe and hippocampus	N/A
3	2	CT showed patchy bi-basilar consolidations	WBC 10.49×10^9/L, Neut 6.63×10^9/L, Lym 2.86×10^9/L, PLT 83×10^9/L; CRP 55 mg/L	WBC 960 cells/mm^3, 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	X-ray did not show any pathological findings	high WBC count 12.9×10^9/L; high procalcitonin 0.10 ng/mL; high D-dimer 0.790 mg/L	N/A	SARS-CoV-2 RNA PCR in CSF (+)	A right frontal intracerebral hematoma associated with subarachnoid hem orrhage 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	19	CT showed ground glass opacities in the bilateral inferior lobes	WBC count 5.96×10^9/L, lymphocytopenia 1.1×10^9/L, PLT 143×10^9/L; CRP 53.2 mg/L	N/A	N/A	MRI revealed an abnormal hyperintensity in the SCC on diffusion-weighted image	N/A
7	20	CT showed right lower lobe infiltrate	N/A	Pressure 30 cmH_2O, nucleated 115 cells/mm^3, erythrocytes 7374 cells/mm^3, 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	N/A	Pressure 48 cm H_2O, no pleocytosis, erythrocytes 27 cells/mm^3, 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
9	20	CT showed multifocal,	N/A	Normal opening pressure; levels of	Markedly increased	MRI showed an equivocal non-enhancing area of fluid-	N/A

		patchy, ground glass opacities		nucleated cells, erythrocytes, and protein within reference levels; increased glucose level	levels of IgM for SARS-CoV-2 S1, SARS-CoV-2 RNA in CSF (-)	attenuated inversion recovery abnormality in the right temporal lobe	
10	21	N/A	N/A	Red cell 921 cells/mm^3, WBC 16 cells/mm^3, neutrophils 8%, protein 0.97 g/L, glucose 92 mg/dL	SARS-CoV-2 RNA in CSF (-)	CT was negative	EEG noted frontal intermittent delta activity
11	22	CT showed multiple peripheral patchy ground-glass opacities	ANA = 2.7, positive; WBC 20 × 10^9/L, Neut 15 × 10^9 /L, Lym 0.8 × 10^9/L, PLT 168 × 10^9/L; CRP 480 mg/L	Protein 0.19 g/L, glucose 61 mg/Dl with no white or red blood cells; HSV-DNA (-)	SARS-CoV-2 RNA in CSF (-)	MRI revealed T2- FLAIR high signal intensities in bilateral thalami, medial temporal and pons. Corresponding areas in T1 images were hypo-signal	N/A
12	37	CT was normal	Blood cell counts, transaminases, bilirubin, CPK, coagulogram, electrolytes, renal function, and CRP were all normal	WBC 1 cell/mm^3, protein 0.32 g/L, glucose 68 mg/dL	SARS-CoV-2 RNA in CSF (+)	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	N/A
13	23	X-ray showed a right lower zone consolidation	WBC 7.0 × 10^9/L, lymphocytes 1.2 × 10^9/L; high CRP 50 mg/L; high GGT 107 U/L, high ALT 88 U/L	Protein 0.423 g/L with no rise in white cells and negative bacterial cultured	Low volume sample could be obtained and PCR for SARS-CoV-2 RNA was not possible	MRI of the brain and cervical spine suggested an inflammatory rhombencephalitis/myelitis, the increased signal lesion in the right inferior 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	N/A
14	24	X-ray and CT were normal	WBC 7.1 × 10^9/L	white cells 70 cells/mm^3 with 100% lymphocyte, protein 0.1 g/L, glucose 120 mg/dL	Unable to send CSF specimen for SARS-CoV-2 RNAPCR testing	CT of the head without contrast was normal	EEG showed generalized slowing with no epileptic discharges
15	25	N/A	N/A	Leukocyte 1 cell/mm^3, protein 0.66 g/L, glucose 10.5 mmol/L	SARS-CoV-2 RNA in CSF (-)	MRI revealed hyperintensity of the right orbital prefrontal cortex adjacent to the olfactory bulb, which seemed to spread towards the right mesial prefrontal cortex and to the right caudate nucleus	EEG showed repetitive 1 Hz rhythmic bursts over the right frontal region, suggestive of a non-convulsive status epilepticus
16	26	CT showed multiple subpleural ground glass opacities	WBC 26.53 × 10^9/L, PLT 202 × 10^9/L; CRP 135 mg/L; D-dimer 6.27 mg/L; LDH 560 IU/L; IL-6 481 pg/mL; ferritin 1763 ng/mL	Protein 0.376 g/L, glucose 130 mg/dL, cell count 0, CSF IgG mg/L -, IgG index -, AlbQ -, oligoclonal band -	SARS-CoV-2 RNA in CSF (-)	MRI findings showing cortical or white matter hyperintensities, contrast enhancement, and sulcal hemorrhagic features, all of which are considered compatible with meningoencephalitis	N/A
17	26	CT showed multiple subpleural ground glass opacities	WBC 20.21 × 10^9/L, PLT 540 × 10^9/L; CRP 82.9 mg/L, D-dimer 6.6 mg/L, LDH 304 IU/L, IL-6 - pg/mL, ferritin 2918 ng/mL	Protein 0.732 g/L, glucose 201 mg/dL, cell count 0, CSF IgG mg/L 4.27, IgG index 0.330, AlbQ 13.5, oligoclonal band none	SARS-CoV-2 RNA in CSF (-)	MRI findings showing cortical or white matter hyperintensities, contrast enhancement, and sulcal hemorrhagic features	N/A
18	26	CT showed multiple	WBC 17.081 × 10^9/L, PLT	Protein 0.657 g/L, glucose 121 mg/dL,	SARS-CoV-2 RNA in	MRI was normal	N/A

		subpleural ground glass opacities	140 × 10^9/L, CRP 32.7 mg/L, D-dimer 0.73 mg/L, LDH 414 IU/L, IL-6 - pg/mL, ferritin 896 ng/mL	cell count 0, CSF IgG mg/L 4.68, IgG index 0.45, AlbQ 8.87, oligoclonal band none	CSF (-)		
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 - pg/mL, ferritin 612 ng/mL	Protein 0.131 g/L, glucose 120 mg/dL, cell count 0, CSF IgG 3.23 mg/L, IgG index 0.780, AlbQ 5.14, oligoclonal band none	SARS-CoV-2 RNA in CSF (-)	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	SARS-CoV-2 RNA in CSF (-)	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 0.57g/L, glucose 59 mg/dL, cell count 0, CSF IgG 5.71 mg/L, IgG index 0.520, AlbQ 10.0, oligoclonal band none	SARS-CoV-2 RNA in CSF (-)	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	N/A
23	27	X-ray showed moderate bilateral interstitial pneumonia	High D-dimer 0.968 mg/L	Lymphocytic pleocytosis 18 cells/mm^3, 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/mm^3, 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 ng/mL; D-dimer 0.625 mg/L; LDH 1016 U/L	WBC count 8 cells/mm^3; protein 0.2 g/L; oligoclonal band test (-)	SARS-CoV-2 RNA in CSF (-)	CT showed hypodensity of the splenium of the corpus collosum	EEG showed mild diffuse slowing
27	29	N/A	CRP 31.3 mg/L; ferritin 1192 ng/mL; D-dimer 0.494 mg/L; LDH 900 U/L	WBC count 2 cells/mm^3; 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 collosum (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 H_2O, cell count 1 cell/mm^3, protein 0.275 g/L, glucose 3.14	SARS-CoV-2 RNA in CSF (-)	CT did not reveal significant abnormalities	N/A

		with multiple fibrous cord-like shadows in both lungs	neutrophil 62.8%; CRP 10.74 mg/L	mmol/L; chloride 123 mmol/L			
29	31	CT showed multiple subpleural ground glass opacities	N/A	Bacteria/HSV type 1 and 2/varicella zoster virus/West Nile virus (-)	Unable to test SARS CoV-2 in the CSF	MRI showed acute necrotizing encephalitis were seen in the bilateral thalami, medial temporal lobes, and sub-insular regions	N/A
30	18	N/A	N/A	N/A	SARS-CoV-2 RNA in CSF (+)	CT was normal	N/A
31	33	N/A	D-dimer 1.8 mg/L	CSF matched oligoclonal band	SARS-CoV-2 RNA in CSF (-)	MRI brain normal	N/A
32	33	N/A	D-dimer 1.599 mg/L	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 subcorticalcerebral white matter	N/A

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[32]. The widespread effects of COVID-19 include neurological disorders, but there have been no detailed clinical reports of their nature to date[33,34]. 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[35,36]. About 80% of COVID-19 patients have no or only mild symptoms, especially in children and young adults. Up to 20% patients with SARS-CoV-2 infection will develop some degrees of severe symptoms[15]. Severe patients were more likely to have neurological complications such as encephalitis, meningitis, stroke, and encephalopathy than non-severe patients[10]. 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[1]. 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, radiology, 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* (%)	

Increased pressure /total	2/5 (40)
Increased protein level /total	13/22 (59.09)
Increased white-cell count level/total	9/23 (39.13)
Ab anti NMDAR (positive), *n* (%)	1 (3.13)
Oligoclonal band test (positive), *n* (%)	1 (3.13)
Neuroimaging, *n* (%)	
Negative/total	12/31 (38.71)
Positive/total	19/31 (61.29)
Not available	1 (3.13)
Results of EEG, *n* (%)	
Diffuse slow wave/total	8/10 (80)
Focal epileptic wave/total	2/10 (20)
Generalized delta activity/total	1/10 (20)
N/A	20 (62.5)
Treatment modality, *n* (%)	
Antibiotics/total	22/28 (78.57)
Antiretroviral drug/total	14/28 (50)
Hydroxychloroquine/total	12/28 (42.86)
Corticoid/total	7/28 (25)
IVIg/total	6/28 (21.43)
Plasmapheresis treatment/total	6/28 (21.43)
Anticonvulsant medications/total	6/28 (21.43)
Surgery/total	1/28 (3.57)
Interleukin-1 receptor antagonist/total	1/28 (3.57)
Traditional Chinese medicine/total	1/28 (3.57)
Not available/total	4/32 (12.5)
Outcome and prognosis, *n* (%)	
Good	21/32 (65.63)
Poor	5/32 (15.64)
Dead	3/32 (9.38)
Not available	3/32 (9.38)

WBC: White blood cell; CRP: C-reactive protein; IL-6: Interleukin-6; CSF: Cerebrospinal fluid; EEG: Electroencephalography; IVIg: Intravenous immune globulin.

treatment to improve the end result.

Encephalitis/meningitis is the neurological complication in patients with SARS-CoV-2 infection[7]. During the ongoing pneumonia epidemic, a few isolated case (patients 4, 12, and 22) reports of SARS-CoV-2 associated encephalitis/meningitis, has been detected the SARS-CoV-2 in CSF[17,37-39]. The medical team of Beijing Ditan Hospital confirmed the presence of SARS-CoV-2 in the CSF of COVID-19 patients through genome sequencing, thus clinically confirming SARS-CoV-2 viral encephalitis[19]. This provides a solid foundation for coronavirus encephalitis. Transcribrial 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[6]. Anosmia and abnormal brain function can help distinguish it from other encephalopathy[9].

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[1]. 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[12]. 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[41]. Among inflammatory markers in patients with SARS-CoV-2 associated encephalitis/meningitis, high WBC count (47.62%), 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[43,44]. 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[45,46]. 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[47]. 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[48]. 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[50,51].

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[38]. 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[52]. 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[53].

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[54,55].

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

entities[56]. 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[57].

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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