

COVID-19-associated meningoencephalitis: A care report and literature review

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Abstract. Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may target the central nervous system and several neurological symptoms have been reported in patients with coronavirus disease 2019 (COVID-19). In the present study, a case of a SARS-CoV-2 complicated with meningoencephalitis was reported. Cerebrospinal fluid (CSF) analyses indicated hyperproteinorrachia but the specimen was negative for SARS-CoV-2 RNA. Furthermore, 10 published articles reporting on patients with COVID-19-associated meningitis/encephalitis were reviewed. Patients diagnosed with COVID-19-associated meningitis/encephalitis had diverse clinical neurological manifestations, including consciousness disturbance, epileptic attacks, psychotic syndrome and meningeal irritation signs. CSF tests revealed elevated protein, lymphocytes and cytokines. SARS-CoV-2 may be detected in the CSF of certain cases. Neuroimaging findings included hyperintense signal changes in the white matter and enhancement of meninges on brain MRI. Certain patients responded well to corticosteroid therapy and had a favorable prognosis, while elderly patients tended to have poor outcomes due to multiple organ dysfunction.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is characterized by respiratory tract symptoms with potentially severe outcomes. It has been reported by epidemiological studies that COVID-19 presents in the majority of cases with

upper respiratory symptoms (1). Recently, studies have reported neurological manifestations of COVID-19 in China in up to 36.4% of hospitalized patients, including alteration of consciousness, headache, dizziness and delirium (2-4). The therapy for COVID-19 remains to be established, although non-pharmacological and preventive treatments have been recommended (5). Like other coronaviruses, SARS-CoV-2 is neurotropic (6). Neurological complications of COVID-19 include cerebrovascular disease, meningitis/encephalitis, acute necrotizing hemorrhagic encephalopathy and Guillain-Barré syndrome (7). However, the clinical characteristics of COVID-19-associated meningitis/encephalitis remain to be defined. Anosmia/dysgeusia has been reported by COVID-19 patient (8-10). This phenomenon provided a hypothesis that COVID-19-associated CNS infection is manifests through a nasopharyngeal route. The present study reported on a patient with COVID-19 presenting with meningio-encephalitis. The clinical characteristics and laboratory results of the patient were investigated. In order to understand the features of COVID-19-associated CNS infection, the literature on COVID-19-associated meningitis/encephalitis cases was reviewed and summarized.

Case report

Data collection. The patient provided informed written consent for the publication of the present case report. The diagnostic/therapeutic procedures applied were in accordance with institutional and international guidelines for the protection of human subjects. The study was approved by the ethics committee of the China-Japan Friendship Hospital (permit no. 2019-183-K124). Clinical and auxiliary test results were retrieved by the authors. Viral/bacterial detection was performed by real-time reverse transcription-PCR (RT-PCR).

Literature search. Entries related to COVID-19-associated encephalitis/encephalopathy were searched in the PubMed, Chinese National Knowledge Infrastructure (CNKI) and EMBASE databases. Articles that were published between December 2019 and 1st June 2020 were specifically screened to ensure the relevance of the results. The following search terms

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were used: COVID-19, SARS-CoV-2, encephalitis, encephalopathy and meningoencephalitis. A total of 44 articles were retrieved. Case reports or case series that provided detailed clinical information were included. Cohort studies, systematic reviews, meta-analyses and clinical trials were excluded. Of note, no relevant articles were found in the CNKI database. A total of 13 articles met the criteria (11-23). Of these, 1 case of COVID-19 diagnosed with herpes encephalitis (21), 1 study that investigated patients with COVID-19 who did not regain consciousness after withdrawal of invasive mechanical ventilation (23) and another study reporting 2 patients diagnosed with COVID-19 pneumonia complicated by minor neurological symptoms but without neurological imaging or lumbar puncture data (22) were excluded. Thus, a total of 10 articles were finally included in the present study. Of note, due to the rapid spread of the COVID-19 epidemic, other relevant articles may have been published during the preparation of the manuscript of the present study.

Results

Case presentation. The case was a 90-year-old female of Han Chinese ethnicity who lived in Wuhan city (China) prior to disease onset. She had a history of cerebral lacunar infarction but with no neurological deficits. She was not self-reliant and lived in a health care unit. The patient developed a fluctuating fever with temperature range between 37.5-38.5°C, severe cough, sputum, fatigue, chest tightness and shortness of breath on the 1st February 2020. A nasopharyngeal swab was taken and SARS-CoV-2 RNA was detected by RT-PCR (24). The patient had a clear consciousness at admission. The patient's breathing tone was coarse on auscultation and neurological examinations were negative. The blood test results are presented in Table I. The patient presented with elevated CRP and decreased lymphocyte number.

The patient exhibited gradual improvement with absorption of the ground glass opacity on chest CT (Fig. 1A). 25 days after disease onset, the patient suddenly became unconscious and the Glasgow Coma Scale score was determined to be 6. On neurological examination, the patient was irresponsive to voice and painful stimulation, her pupils were isochoric (2-mm diameter) and reactive, and there was no autonomous activity in any limbs. There were significantly increased muscle tension, positive cortico-spinal tract signs on both sides, a positive meningeal irritation sign, obvious neck stiffness, and a positive Kernig sign. Brain CT was unremarkable compared with a previous brain MRI (Fig. 1B); however, the patient was not subjected to brain MRI at this time-point.

Considering the probable diagnosis of meningoencephalitis, the patient received mannitol and anti-viral therapy (Ganciclovir). A lumbar puncture on March 6th 2020 (10 days after unconsciousness) revealed an opening pressure of 60 mmH₂O, cerebrospinal fluid (CSF) cell count with an increased 25/ μ l (10 mononuclear and 15 polymorphonuclear cells without red blood cells) and CSF protein levels were also increased with 660 mg/l (normal range: 120-600 mg/l), but normal glucose, chloride and adenosine deaminase levels. Tests for viral/bacterial pathogens (including varicella zoster virus and herpes simplex virus) in the CSF were negative. The result of RT-PCR detection of SARS-CoV-2 RNA in the CSF

was negative. However, the patient died of gastrointestinal bleeding 46 days after disease onset.

Summary of clinical characteristics. A total of 10 cases from 10 articles were included in the literature review of the present study. The clinical characteristics of the 10 cases are listed in Table II. The age of the patients ranged from 24 to 75 years and the cases included 6 patients aged <60 years. The cases comprised 7 males and 3 females. Only 1 patient had a negative detection result for SARS-CoV-2 RNA in a nasopharyngeal swab. Common neurological signs and symptoms included confusion and coma [patient no. 2 (P2)-5 and P7-9], neck stiffness (P1 and P8), positive meningeal irritation sign (P1, P7), mental disturbance (P1, P2, P4 and P8), seizure (P3 and P6), cognitive impairment (P2 and P4), motor dysfunction (P5 and P10) and psychotic symptoms (P3). A total of four patients exhibited abnormalities on brain MRI, which included cerebellar lesions (P5), lesions of the hippocampus in the temporal lobe (P6), cerebral hemorrhage, subarachnoid hemorrhage accompanied by bilateral supratentorial leptomeningeal enhancement (P9) and hyperintensity in the corpus callosum of splenium (P10).

A total of nine cases received lumbar puncture examination, with increased intracranial pressure in only 3 cases (P1, P6 and P7). The CSF protein level was mildly increased in most cases. CSF cytology indicated a slightly increased proportion of white blood cells (WBC) and lymphocytes. Only 3 cases presented with positive SARS-CoV-2 in the CSF (P6, P8 and P9). The patients were negative for other CSF infections and autoimmune antibodies. P2 exhibited increased cytokines (IL-6, IL-8 and TNF- α) in the CSF and exacerbation clinically. For treatment, corticosteroid therapy and mannitol infusion along with antiviral therapy were administered in some of these 10 cases. Good prognosis and neurological recovery were observed in 6 patients (P1-3 and P7-9), while 2 patients had mild remaining symptoms (P4 and P5). However, elderly patients tended to have poor outcomes and the oldest patient died (P10).

Discussion

The present study reported on a patient who developed meningoencephalitis after being diagnosed with SARS-CoV-2 infection. The patient gradually recovered from the respiratory symptoms prior to the onset of neurological symptoms. However, the patient suddenly became unconscious and developed neck stiffness and positive cortico-spinal tract signs in all limbs. CSF analysis suggested infection of the central nervous system (CNS) with elevated WBC. A screen for usual pathogens (bacterial, fungal and viral), including SARS-CoV-2, was negative. Based on recently reported diagnostic criteria (25), a possible diagnosis of COVID-19-associated encephalitis was made. Furthermore, published cases of COVID-19-related encephalitis (until 2020 July) were reviewed and their clinical characteristics were summarized. Neurological features mostly started from the time of respiratory symptom onset to 30 days thereafter. The neurological manifestations included irritability, confusion, reduced consciousness and seizures.

As other coronaviruses (7), SARS-CoV-2 is neurotropic. SARS-CoV-2 has been postulated to enter the CNS via

Table I. Laboratory data of the patient with COVID-19 pneumonia with subsequent meningoencephalitis.

Parameter (normal range)	Day of COVID-19 symptoms			
	6	20	27	34
Hemoglobin (g/l, 115-150)	119	119	109	117
WBC ($10^9/l$, 3.5-9.5)	3.46	5.86	11.14	9.4
Neutrophils ($10^9/l$, 1.8-6.3)	1.52	4.33	10.07	8.84
Lymphocytes ($10^9/l$, 1.1-3.2)	1.37	0.94	0.81	0.34
Monocytes ($10^9/l$, 0.1-0.6)	0.56	52	0.23	0.17
Platelets ($10^9/l$, 125-350)	104	217	225	73
Sodium (mmol/l, 133-146)	138	140	152	146
Potassium (mmol/l, 3.5-5.3)	3.81	3.9	3.1	2.88
Blood urea nitrogen (mmol/l, 3.1-8.8)	4	3.5	9.18	7.34
Creatinine (mol/l, 41-81)	52	37	37	36
Corrected calcium (mmol/l, 2.1-2.37)	2.47	2.49		2.18
ALT (U/l, 7-40)	13	11		37
Total bilirubin (μ mol/l, 0-23)	5.8	10.3		24
CRP (mg/l, 0.0-10)	18.2	6	22.6	12
PCT (ng/ml, <0.1)	0.107	0.045		0.316
D-dimer (ng/ml, <500)	0.63		1.21	
Creatine kinase (U/l)	68		25	590
TnI (ng/ml, 0-0.04)				0.382

ALT, alanine transaminase; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell count; TnI, troponin I.

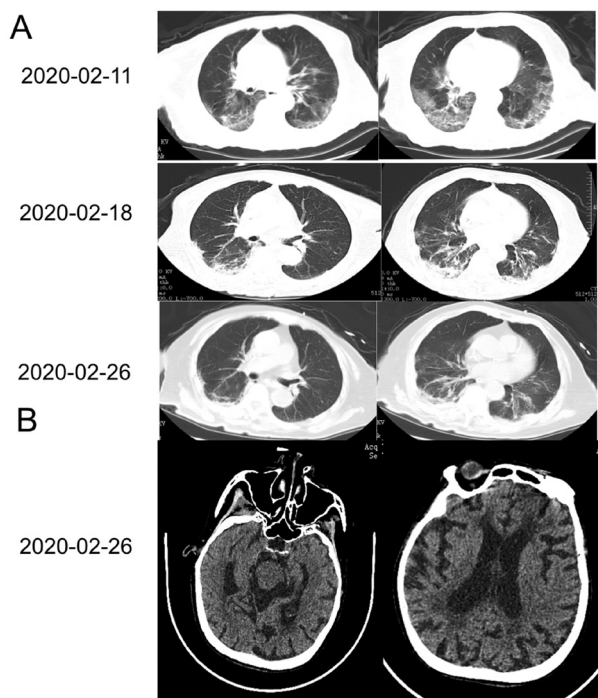


Figure 1. Representative CT and MRI images of the patient. (A) Chest CT images revealed bilateral GGO and segmental areas of consolidation at 11 days after disease onset. These GGOs were gradually resolved by days 18 and 26 after disease. (B) The head CT on the day that the patient entered the coma, which did not present any remarkable findings. GGO, ground-glass opacity.

hematogenous spread from the systemic circulation to the cerebral circulation, and via dissemination through the cribriform plate and olfactory bulb (26). Furthermore, SARS-CoV-2 was reported to enter the CNS via binding to angiotensin converting enzyme 2 expressed in the capillary endothelium of the blood-brain barrier (27). SARS-CoV-2 RNA was detected in the CSF of 3 patients with COVID-19 reported in the literature review, of these 3 patients, 2 patients presented with abnormal neuroimaging findings. SARS-CoV-2 may also reach the CNS via trans-synaptic propagation through the nasal cavity. This neuronal approach is consistent with the clinical observation that certain patients with COVID-19 develop anosmia (28). However, there was no evidence of anosmia/dysgeusia in the cases reviewed.

Certain cases included in the present literature review were in a hyperinflammatory state secondary to SARS-CoV-2 infection, with massive release of cytokines and chemokines. Patient 2 in Table II and another 2 previously reported cases (29) had obvious elevation of CSF cytokines accompanied by exacerbation of neurological symptoms. Acute necrotizing encephalopathy was also recently reported in patients with COVID-19 (30). Thus, a hyperinflammatory state secondary to infection may have an important role in CNS injury by SARS-CoV-2.

The present analysis indicated that SARS-CoV-2 infected meningitis/encephalitis had a relatively non-fatal process with complete clinical recovery in the majority of cases. Specifically, almost 60% of patients exhibited neurological recovery, but with certain symptoms remaining, including

Table II. Clinical characteristics of reported SARS-CoV-2-induced encephalitis/meningitis cases in the literature.

Patient no.	Author (year)	Sex	Age (years)	NPS	Neurological symptoms	Brain CT/MRI	CSF	Therapy and outcome	(Refs.)
1	Yin (2020)	M	64	+	Lethargic and irritability; dissociated speech; neck stiffness, meningeal irritation signs	(-)	Opening pressure, 200 mmH ₂ O; cell count, 1 ^a , protein 275.5 ^b , SARS-CoV2 (-)	Antiviral therapy; Recovery and discharge	(11)
2	Pilotto (2020)	M	60	+	Irritability; confusion and asthenia; cognitive fluctuations; akinetic syndrome	(-)	Lymphocytes, 18 ^a ; protein, 696 ^b ; viruses (-); IL-6, IL-8, TNF- α elevated; tau (-); NFL (-)	Methylprednisolone 1 g/day for five days; Normal neurological examination	(12)
3	Bernard Valnet (2020)	F	64	+	Psychotic symptoms; seizure; disorientation; attention deficit; bilateral grasping	(-)	^c Protein, 466/399 ^b ; cells, 17/26 ^c ; lymphocyte (%), 97/100; viruses/bacteria (-); anti-neuronal antibodies (-); SARS-CoV-2 (-)	Antiviral therapy; Resolution of symptoms 96 h after admission	(13)
4	Bernard Valnet (2020)	F	67	+	Headache; drowsiness; confusion, disorientation; bilateral grasping; aggressiveness; hemianopia; sensory hemineglect	(-)	^c Protein, 461/485 ^b ; cells, 21/6 ^a ; lymphocyte (%), 89/82; viral/bacterial pathogens (-); anti-neuronal antibodies (-); SARS-CoV-2 (-)	Antiviral and anti-bacterial therapy; Symptoms resolved within 24 h, except for a mild headache	(13)
5	Wong (2020)	M	40	+	Consciousness disturbance; diplopia, ataxia; altered sensation; hiccups and dribbling	Lesion in the inferior cerebellar peduncle and the upper cord	Protein, 423 ^b ; no increase in white cells and negative bacterial culture; SARS-CoV-2 RNA ND	Not mentioned in therapy; Improvement in hiccups and nystagmus but oscillopsia and ataxia persisted	(14)
6	Moriguchi (2020)	M	24	-	Multiple epileptic seizures; GCS score 6; neck stiffness	Hyperintensity in the mesial temporal lobe and hippocampus	Opening pressure is 320 mmH ₂ O; mononuclear cells, 10 ^a , polymorphonuclear cells, 2 ^a ; other viruses (-); SARS-CoV-2 (+)	Antiviral and anti-bacterial therapy, steroids; Impaired consciousness at day 15	(15)
7	Ye (2020)	M	Not stated	+	Sudden confusion; meningeal irritation signs; extensor plantar response	(-)	Opening pressure is 220 mmH ₂ O; protein, 270 ^b ; SARS-CoV-2 (-)	Mannitol antiviral therapy; Consciousness became clear	(16)
8	Huang 2020 and Duong (2020)	F	41	+	Neck stiffness; photophobia; confusion, agitation, disorientation and hallucinations; no respiratory involvement	(-)	White cells, 70 ^a (100% lymphocytes); protein, 100 ^b ; SARS-CoV-2 (+)	Antiviral and hydroxychloroquine; Mental status gradually improved without neurological deficits	(17,19)

Table II. Continued.

Patient no.	Author (year)	Sex	Age (years)	NPS	Neurological symptoms	Brain CT/MRI	CSF	Therapy and outcome	(Refs.)
9	Al-olama (2020)	M	36	+	Drowsiness and mild confusion; GCS score 13	ICH, SAH in frontal and temporal lobes; bilateral supratentorial leptomeningeal increased enhancement	Fluid from the chronic subdural hematoma tested SARS-CoV-2 (+)	Not mentioned in therapy; Neurologically stable	(18)
10	Hayashi (2020)	M	75	+	Tremor in hand; walking instability; urinary incontinence; mild ataxic gait	Abnormal hyperintensity in the SCC on DWI	ND	Corticosteroid pulse, antiviral and; anti-bacterial therapy Neurologically recovered but died at last	(20)
The present case	Pu (2020)	F	90	+	Consciousness disturbance; GCS score 6; neck stiffness, meningeal irritation signs	(-)	Opening pressure is 60 mmH ₂ O; protein, 660 ^b ; 10 mononuclear and 15 polymorphonuclear cells; SARS-CoV-2 (-)	Died at last and without neurological recovery	-

^aCSF cell number presented in units/mm³; ^bunits for CSF protein levels are mg/l; ^ctwo times lumbar puncture. NPS, nasopharyngeal swab; CSF, cerebrospinal fluid; ND, not determined; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; GCS Glasgow Coma Scale; SCC, corpus callosum of splenium; DWI, diffusion weighted imaging; ICH, cerebral hemorrhage; SAH, subarachnoid hemorrhage; NFL, neurofilament light.

headache. This suggests that SARS-CoV-2 may induce a viral encephalitis or aseptic meningitis. With viral clearance and use of corticosteroids, the CSF pressure was gradually reduced and the neurological manifestations gradually improved. Immunoinhibition therapy is effective for reducing CSF cytokines and associated neurological manifestations. The present analysis suggested a role for cytokine-mediated neuroinflammation in these patients. Of note, senior patients (>60 years old), those positive for SARS-CoV-2 RNA in the CSF and those with brain MRI abnormalities tended to have poor outcomes.

In conclusion, COVID-19 infection may be associated with meningitis/encephalitis. The initial symptoms vary, although changes in consciousness, seizures and meningeal irritation signs were most frequent. Furthermore, CSF protein and white cell levels were typically elevated, with positive SARS-CoV RNA and elevated cytokine levels in the CSF in certain patients. Of note, most cases had favorable outcomes, except for older patients. A limitation of the present study was the lack of brain MRI in certain patients, including the present case. However, MRI was difficult to perform in certain patients due to medical isolation during the COVID-19 pandemic. Another limitation was that inflammatory cytokines in the CSF were not examined in the present case, which would have been required to confirm the disease pathogenesis.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

PL and XPW contributed to the conception and design of the study. FP contributed to the acquisition and analyses of data. PL performed the literature review. YZ, LZ, LS, YW, NL, PH and TH contributed to analyzing and drafting the manuscript. PL, YZ, LZ and LS contributed to preparing the figures. PL and XPW check and confirm the raw data of the study. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was approved by the ethics committee of the China-Japan Friendship Hospital (Beijing, China).

Patient consent for publication

The patient's guardians provided informed written consent for the case report.

Competing interests

The authors declare that they have no competing interests.

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