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Case report

Correlation between CSF biomarkers and COVID-19 meningoencephalitis: A case series

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ABSTRACT

Background: Recent studies have focused on the incidence rate and pattern of meningoencephalitis in the coronavirus disease 2019 (COVID-19).
Aim: This study aims to shed more light on the CSF pattern and clinical characteristics of meningoencephalitis COVID-19 patients in Zanjan, Iran.
Methods: Nine cases of laboratory and imaging confirmed COVID-19 were admitted to Valiasr Hospitals in Zanjan, Iran. Data were collected from May 20, 2020 to June 20, 2020.
Results: All the nine patients had positive RT-PCR COVID-19 and Pulmonary involvement who underwent Lumbar puncture and analysis, but despite neurological symptoms, the RT-PCR of CSF for COVID-19 was negative.
Conclusion: Although we did not have any cases of positive RT-PCR for COVID-19 in lumbar puncture specimens, the justification of neurological symptoms in patients can be the transient presence of the virus in the CSF, and inflammation or autoimmune response caused by the virus, so more studies are needed to determine the cause of neurogenic symptoms.

1. Introduction

Studies carried out since the COVID-19 outbreak have revealed conflicting statistics on the incidence of meningoencephalitis in various countries. In one national registry of 125 patients with COVID-19 and neurological or psychiatric disease reported over a 3-week period, 31% patients had altered mental status, which included 13% with encephalopathy (of whom 6% had encephalitis) [1]. In 214 patients (in three centers in Wuhan, China) of whom 58.9% had non-severe COVID-19 and 41.1% had severe COVID-19 infection, 36.4% patients had neurological manifestation. In patients with CNS manifestations, the most common reported symptoms was dizziness (16.8%). Moreover, nervous system manifestations were significantly more common in severe compared with non-severe (45.5% versus 30.2% with P value = 0.02) [2]. It is currently believed that COVID-19, together with the host's immune mechanisms, can transform these infections into persistent nervous system infections that can lead to neurological illnesses. Timely cerebrospinal fluid (CSF) analysis and management of neurological complications associated with infections are key to improving the prognosis of critically ill patients [3]. We aimed to evaluate the incidence of meningoencephalitis in 8 patients with COVID-19 who presented with impaired level of consciousness and other neurological symptoms.

2. Methods

We included patients with COVID-19-confirmed infection who had neurological symptoms, followed by a diagnostic lumbar puncture (LP) and if leukocytes were present in CSF, viral and bacterial causes were evaluated. All patients were admitted in Valiasr University Hospital in Zanjan, Iran, between May 20th, and June 20th, 2020. Patients were selected for LP with clinical indications including: decreased level or content of consciousness, focal neurological deficit, fever and headache, and seizure. For all patients, we performed COVID-19 real-time reverse-transcriptase polymerase chain reaction (RT-PCR), spiral lung CT scan, brain CT and MRI, and expert radiologist report was obtained. The

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Table 1
Patients' characteristics at baseline.

Patient number	Sex	Age	Comorbidities	Neurological signs and symptoms	o_2 saturation	CRP Mg/L	Creatinine	Lymphocyte Count	Platelet	Outcome
1	M	71	DM, HLP	Loss of consciousness	85%	30.5	2.1	793	182000	Death
2	M	65	–	Left hemiparesis	90%	31.5	1	866	35000	Death
3	M	89	HTN	Left hemiparesis and Dysarthria	87%	40	1.2	864	154000	Death
4	M	15	CP	Fever and seizure	92%	25	1.8	386	109000	Discharge
5	F	81	–	Agitation and disorientation to time and place, exhibited poor memory, difficulty with fluent speech	91%	30.3	1	168	140000	Discharge
6	F	60	CHF, HTN, DM	Fever, nausea, vomiting and lack of awareness	81%	35	0.8	227	136000	Discharge
7	F	69	DM, CKD, HTN	Fever and lack of awareness	88%	32	2.2	954	90000	Death
8	M	62	COPD, HTN	Loss of consciousness	94%	33	2	331	175000	Death
9	M	78	DM,CKD	loss of consciousness and fever	80%	30.6	2.8	429	97000	Death

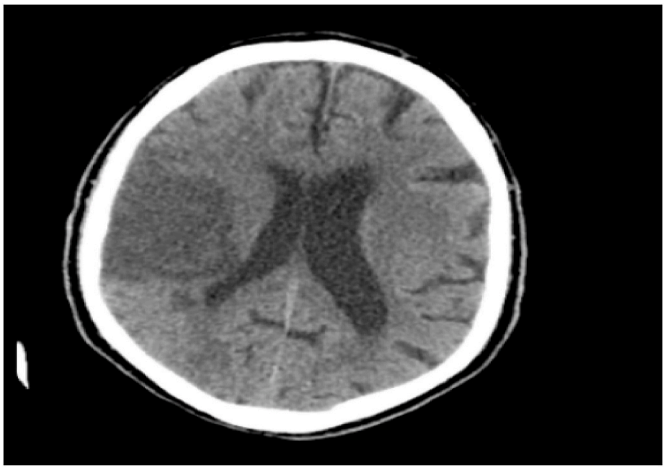

Fig. 1. The patient 3 Brain CT scan after a few days.

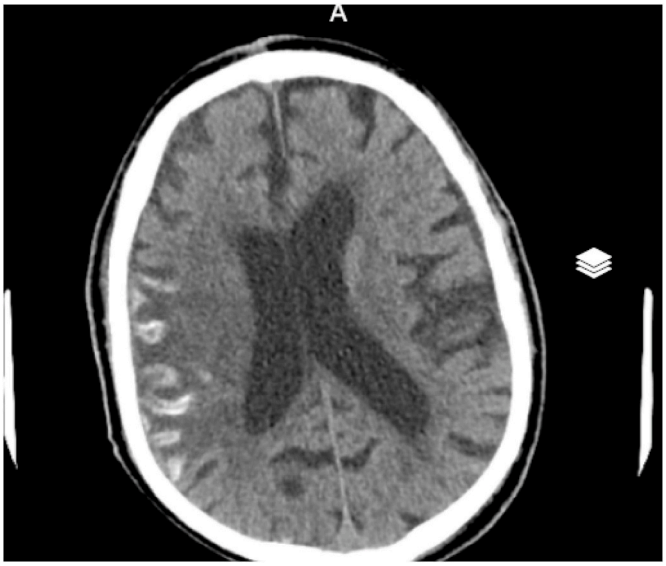

Fig. 2. The patient 3 Brain CT scan after 7 days, hemorrhagic pattern added to ischemic CVA.

Table 2
Patient LP features.

Patient number	Glucose level	Protein level	WBC Count
1	175	24	0–1
2	75	22	0–1
3	70	32	0–1
4	65	18	0–1
5	108	25	0–1
6	100	20	0–1
7	35	50	0–1
8	109	28	0–1
9	171	21	60

method of diagnosis is RT-PCR assay test using throat swab specimens collected from upper respiratory tracts.

3. Data availability

Researchers can apply for anonymzed data access from the present study for well-defined research questions that are in line with the overall research agenda for the cohort. Please contact the corresponding author.

4. Results

In this study, nine patients who had clinical and laboratory data or highly suggestive spiral lung CT scans suspected for COVID-19 underwent a diagnostic LP on clinical indications. Patient characteristics at baseline are shown in Table 1. Four patients had hypertension and three had diabetes mellitus. One of the patients admitted with a focal neurological deficit (hemiparesis) and fever, the brain MRI with DWI showed new CVA. The mean age was 64 years old, mean platelet count 110000 and mean lymphocyte count 570.

PATIENT 2: Presented with dyspnea, left hemiparesis and hematemesis. Brain CT scan and MRI showed old CVA but hemiparesis did not exist before. Upper gastrointestinal endoscopy showed the visible vessel. Patient was intubated and admitted in ICU. Lung spiral CT scan for COVID-19 was highly suggestive (CORAD 5).

PATIENT 3: Presented with fever, left hemiparesis and Dysarthria. Brain CT scan and MRI showed acute CVA (Right Middle Cerebral Artery) (Fig. 1). Lung spiral CT scan for COVID-19 was highly suggestive (CORAD 5). After seven days the hemorrhagic lesion was added(Fig. 2).

PATIENT 4: A 15-year-old boy with past medical history of cerebral palsy presented with fever and seizure. The patient had no history of seizure. Lung spiral CT scan for COVID-19 was indeterminate (CORAD 3).

The characteristics of the other six patients are listed in the tables. All patients' cultures were negative. CSF sample for herpes virus and

tuberculosis was also negative. Brain CT scan showed generalized atrophy, and only small vessel disease was reported in Brain-MRI [4].

All of the nine patients had positive RT-PCR for COVID-19.

5. CSF viral detection and biomarkers

RT-PCR performed on cerebrospinal fluid for COVID-19 was negative. None of the patients had CSF pleocytosis (WBC $\leq$3 cells/μL) (except number 9 patient): glucose and protein level are shown in Table 2.

6. Discussion

In our study, the most common clinical symptom of patients was a decrease in level of consciousness (50% in four patients). In some other studies, the most common clinical sign was dizziness [2,5]. Examination of patients' CSF sugar level revealed that two patients had abnormal CSF sugar. One patient had 60 count leukocytes in the CSF, which was reported to be negative for other viral and bacterial causes, but for other patients, other viral causes were not investigated due to the lack of leukocytes in the CSF. In the Eden et al. report, the CSF WBC count of six patients with COVID-19 and neurological symptoms was normal in all participants (WBC<3) [6]. RT-PCR performed on CSF of patients for COVID 19 was negative. Likewise, a definitive diagnosis of viral encephalitis depends on the ability to detect or culture the virus from CSF or brain tissue, but this can be difficult as SARS-CoV-2 is transiently disseminated and its titer in CSF can be low [7,8]. This may indicate the absence of the virus in the CSF or the lack of detection of the virus in the CSF by RT-PCR. Even if a direct viral origin cannot be eliminated, the pathophysiology of brain damage related to SARS-COV-2 seems rather to involve an inflammatory or autoimmune response [9]. In the Eden study, SARS-CoV-2 RNA was detectable in plasma in 2 patients and CSF in 3 patients. Due to these low levels of viral detection, all plasma and CSF samples with detectable viral RNA were reanalyzed using the Xpert® assay. Both reruns in plasma confirmed SARS-CoV-2 RNA detection, while SARS-CoV-2 RNA was undetectable in all three CSF samples [6]. Lymphocyte counts in CBC were reported in all patients at below 1100. It is mentioned in a study that the lymphocyte counts were lower for patients with CNS symptoms than those without CNS symptoms, which may be indicative of the immunosuppression in patients with COVID-19 with CNS symptoms, especially in the severe subgroup [2]. All patients had evidence of pulmonary involvement in favor of COVID-19 on pulmonary CT in addition to neurological symptoms. Five patients died (62.5%), and three were discharged (37.5%). None of the patients had leukopenia, but all patients had lymphopenia below 1300 and had a serious clinical condition that could indicate a link between the severity of the disease and the incidence of CNS involvement. Limitations of the study are the small sample size and not including a control group of patients with COVID-19 of comparable severity without neurological manifestations, which can reduce the power of the study.

7. Conclusion

Although we did not have any cases of positive RT-PCR for COVID-19 in lumbar puncture specimens, the justification of neurological symptoms in patients can be due to transient presence of the virus in the CSF, and inflammation or autoimmune response caused by the virus. Therefore, more studies are needed to determine the cause of neurogenic symptoms.

Author contributions

Moghtader, Jozpanahi, Moghimi, Khodadadi, Jafarzade and Abbaspour have equally contributed in designing, reviewing, drafting, analyzing the data and writing the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2020.101335.

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