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Case Report

SARS-CoV-2-Associated Encephalitis: a Case Report

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Abstract

COVID-19 presents with respiratory symptoms and signs in the majority of cases. The central nervous system can be affected directly or indirectly, which is demonstrated by a number of neurological abnormalities and complications. The aim of this study is to present a clinical case of SARS-CoV-2-associated encephalitis and highlight the severity of this neurological illness over the course of COVID-19. Etiological diagnosis methods include examination of the nasopharyngeal swab and cerebrospinal fluid by PCR.

A 45-year-old man with fever, altered consciousness, and tonic-clonic seizures was admitted to the Clinic of Infectious Diseases, St George University Hospital, Plovdiv. The diagnosis of COVID-19 encephalitis is based on typical clinical and laboratory data, positive SARS-CoV-2 PCR, and exclusion of other likely causative agents into the cerebrospinal fluid. The patient was discharged two weeks after admission without neurological sequelae. The case confirms the clinical variety of COVID-19 and the possibility of severe neurological manifestations. Encephalitis is a rare but potentially life-threatening condition. Physicians should be aware of encephalitis in SARS-CoV-2 patients with neurological symptoms.

Keywords

central nervous system, COVID-19, neuroinfection, PCR, seizure

INTRODUCTION

COVID-19 presents with respiratory symptoms and signs in the majority of cases. The nervous system can be affected directly or indirectly, which is demonstrated by a number of neurological abnormalities and complications, including cerebrovascular disease, encephalitis and meningitis, encephalopathy, the Guillain-Barré syndrome, and skeletal muscular symptoms. However, it is challenging to identify whether these neurological symptoms resulted from a central nervous system (CNS) infection rather than have a peripheral origin due to hypoxia, blood clots, and cytokine storm in advanced patients.[1]

Encephalitis is an inflammation of the brain parenchyma caused by a viral pathogen and/or an autoimmune process. Two types can be distinguished according to the pathogenetic mechanism, including virus-induced encephalitis and autoimmune encephalitis. Although it is a rare neurological manifestation of COVID-19 (0.22%), encephalitis is associated with a severe course and significant mortality rate (28.3%).[2]

The possible SARS-CoV-2 neuroinvasion mechanisms

include invasion by the olfactory nerve, direct infection of vascular endothelial cells, and invasion through inducing inflammatory responses that disrupt the blood brain barrier.[1] SARS-CoV-2 encephalitis presents with disturbances in consciousness (77%), fever (64%), seizures (38%), headache (27%), psychosis (15%), and muscle weakness (15%). Less common are aphasia, ataxia, and myoclonus. Respiratory symptoms like cough and shortness of breath manifest 7 to 14 days before encephalitis onset, but they may be absent in 24%.[2] The prognosis is unfavorable. A recovery with residual manifestations is observed in 38%, full recovery in 29%, and death occur in 13.4-20% of cases.[3]

An autoimmune mechanism is involved in about 23% of the cases of COVID-19 encephalitis. Autoimmune encephalitis can occur from a few days to one month post-onset of COVID-19. Diagnostic criteria are the presence of autoimmune antibodies against intracellular neuronal, cell-surface, and synaptic proteins in the CSF and/or serum, as well as elevated CSF protein. The prognosis is relatively more favorable compared to virus-induced encephalitis. 67% of patients recover completely, and only 7% remain with severe long-term or permanent disabilities.[4,5]

The aim of the study is to present a clinical case of COVID-19-associated encephalitis, as well as to emphasize the severity of this neurological syndrome in SARS-CoV-2 infection.

CASE REPORT

A 45-year-old male presented with low-grade fever, vomiting, diarrhea, fatigue, and loss of appetite. He became confused and lethargic 4-5 days after clinical onset. He was admitted to a hospital in severe condition with disorientation, agitation, and no signs of meningeal irritation including neck stiffness, Kernig and Brudzinski's signs. Hyperalgesia, increased tendon reflexes and extended reflexogenic zones were present. Tremor and Babinski's sign were also observed. His respiratory function was normal, and the oxygen saturation was 98%. The heart rate was 93 beats per minute and blood pressure was 120/85 mmHg. The patient had no chronic underlying diseases according to his relatives.

An hour after admission, generalized tonic-clonic seizures occurred accompanied by perioral cyanosis and apnea. Orotracheal intubation and subsequent ventilation were initiated. The chest X-ray was normal. The brain computed tomography (CT) showed an infratentorial hypodense lesion of the pons. Because of multiple seizure episodes and fever over 38.7°C, the patient was transferred immediately to the Intensive Care Unit of Clinic of Infectious Diseases, St George University Hospital in Plovdiv with suspicion of encephalitis.

*Laboratory findings are shown in **Table 1**. Blood tests established a mild anemia, increased inflammatory markers, and glucose levels. Serum electrolytes and liver enzymes were within normal limits: AST 31 U/l; ALT 38 U/l (reference range 0-50 U/l); elevated ferritin 702.02 ng/ml (reference range 18–270 ng/ml), and normal procalcitonin 0.11 ng/ml (reference range <0.5 ng/ml). Coagulation tests revealed elevated D-dimers and fibrinogen levels.*

The urine examination showed presence of protein, glucose and ketones. Glucose levels were strictly monitored during the hospital stay. The blood gas analysis did not reveal any severe deviations related to lung damage including after extubation.

*The lumbar punctures (LP) were performed at admission and 7 days later **(Table 2)**. CSF findings were typical for aseptic inflammation such as elevated protein and glucose. The CSF culture was negative. A multiplex PCR (Biofire, FilmArray, bioMerieux) for bacterial, viral and fungal pathogens (S. pneumoniae, S. agalactiae, N. meningitis, L. mono-*

Table 1. Blood parameters

Parameters	Day 1	Day 3	Day 10	Reference range
Hemoglobin, g/l	168	124	122	140–180
White blood cells, $\times 10^9$/l	9.73	8.18†	11.95	3.5–10.5
Platelets, $\times 10^9$/l	244	148	237	140–400
Glucose, mmol/l	14.3	5.6	16.5	2.8–6.1
Erythrocyte sedimentation rate, mm/h	-	20	72	2–15
C-reactive protein, mg/l	3.6	34	26	0–10
Creatinine, μmol/l	77.5	76	67	74–134
Urea, mmol/l	3.7	3.6	2.7	3.2–8.2
Potassium, mmol/l	4.5	3.5	3.6	3.5–5.6
Sodium, mmol/l	139	140	141	136–151
Prothrombin time, %	-	97.7	93.7	70–120
D-dimers, mg/l	-	1.69	0.86	0–0.5
Fibrinogen, g/l	-	5.04	5.76	2–4.4

† Differential count: polymorphonuclear leukocytes 70.5%, monocytes 7.1%, lymphocytes 15.5%

Table 2. Cerebrospinal fluid examination

Parameters	Diagnostic LP Day 1	Control LP Day 7	Reference range
WBC, $\times 10^6$/l	2	18	<6
Protein, g/l	1.79	0.71	<0.45
Glucose, mmol/l	7.8	6.7	2.22-4.44
IgG, mg/l	118	-	0-40

cytogenes, H. influenzae, E. coli K1; cytomegalovirus, herpes simplex virus-1, herpes simplex virus 2, human herpes virus 6, human parechovirus, varicella-zoster virus; Cryptococcus neoformans/gatti) was performed in CSF and none of them was identified. The CSF sample (day 7) was retested for HSV, but the result was also negative.

SARS-CoV-2 was identified by PCR of the nasopharyngeal swab. Blood and nasopharyngeal cultures were negative. Multidrug-resistant Pseudomonas aeruginosa, which was sensitive only to ceftazidime/avibactam and colistin, was isolated from tracheal secretions.

*The second chest X-ray revealed only mild bilateral interstitial inflammation in the lung bases 5 days post admission (**Fig. 1**).*

*Cerebral CT revealed no abnormalities in the brain parenchyma 10 days post admission (**Fig. 2**). Both brain parenchyma and ventricular system were normal. The lesion in pons, which was described on the first CT scan, was not visualized.*

Acyclovir 750 mg 3 times daily was administered because of suspected herpes simplex etiology until a second negative result for HSV was obtained. Antibiotic therapy with ceftriaxone was administered as well as colistin because of Pseudomonas aeruginosa isolation. Dexamethasone for 7 days, mannitol 10%, depakine infusion, anticoagulant, insulin, lisinopril, gastroprotective and symptomatic drugs were used during the disease course.

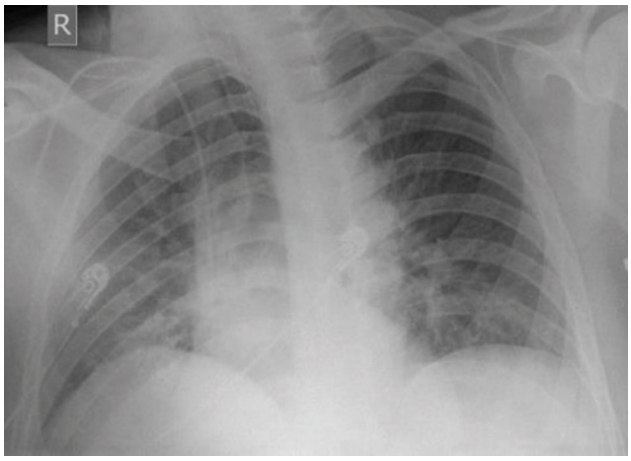

Figure 1. Pulmography

The patient was on mechanical ventilation for 4 days. There were no signs of respiratory failure and no need for O_2 supplementation after extubation. Only mild disturbances in consciousness such as somnolence and bradypsychia persisted for 3-4 days. The patient's condition improved and a full neurological recovery was observed 2 weeks post admission. Increased blood glucose levels, which were registered during the hospital stay, were characteristic for diabetes mellitus.

The diagnosis of COVID-19-associated encephalitis was based on the neurological symptoms and CSF examination as well as on the negative results for common pathogens in

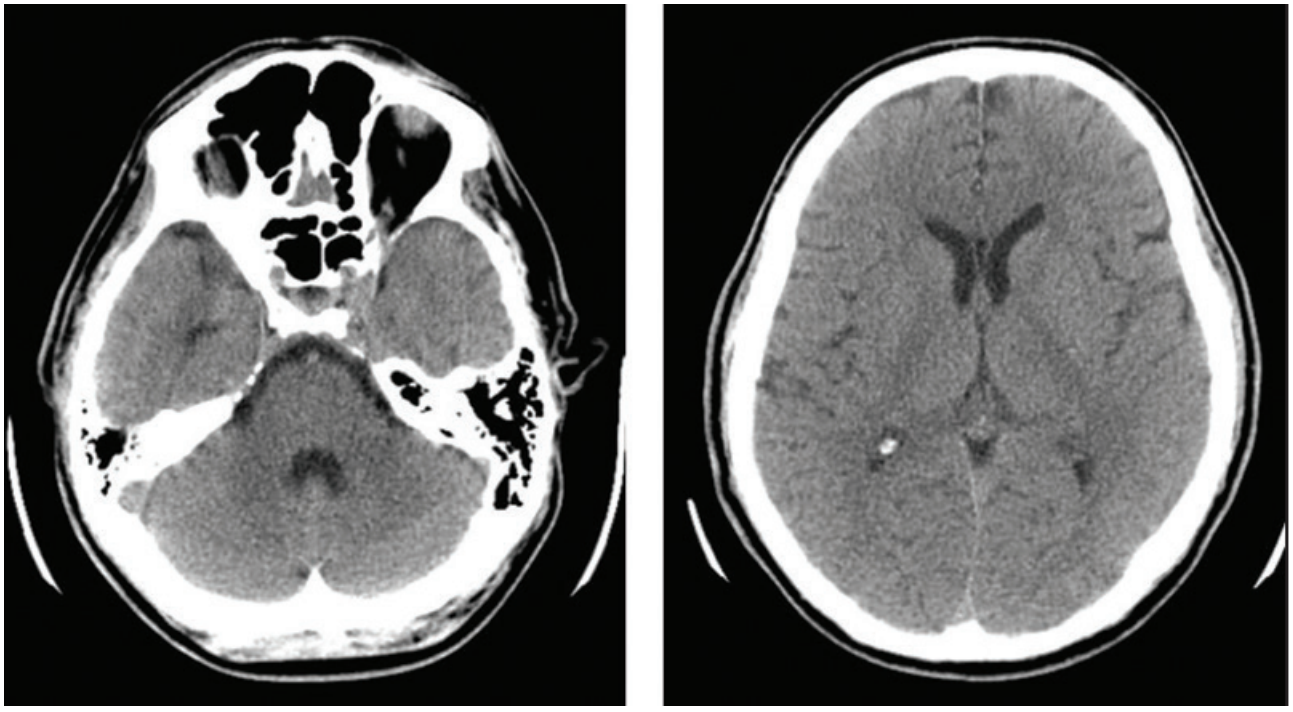

Figure 2. Brain computed tomography.

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CSF in a SARS-CoV-2 positive patient. He was discharged without sequelae and referred to an endocrinologist because of new-onset diabetes.

DISCUSSION

According to a systematic review of CNS infections due to SARS-CoV-2, 59.4% of patients have encephalitis, followed by meningitis (15.6%), meningoencephalitis (15.6%), encephalomyelitis (6.3%), rhombencephalitis (3.1%), and myelitis (3.1%).[6]

COVID-19 encephalitis can be found in all age groups, mainly over 30 years. The incidence is relatively low in children and adolescents, which may be related to the relatively mild illness.[6] The mean age of encephalitis patients is 55 years with almost equal sex distribution. Risk factors are advanced age, severe COVID-19, and comorbidities such as arterial hypertension (45.6%), diabetes mellitus (16%), obesity (12.5%), and chronic neurological diseases (10.4%).[3] Although, our 45-year-old patient had no previously known disease, diabetes mellitus was diagnosed in the course of COVID-19. We can only assume that he had a previously undiagnosed disease that clinically manifested due to the severe infection.

His clinical presentation was typical for viral encephalitis including fever, vomiting, disturbances in consciousness, and seizures. He had no respiratory symptoms. CRP, ferritin, and D-dimers levels in serum are usually elevated in encephalitis patients[7], and these data are similar to our case. Authors report lymphocytic pleocytosis (52.7%) and increased protein concentration (46.3%) in CSF. SARS-CoV-2 can be isolated rarely in CSF by PCR (17%), and specific anti-SARS-CoV-2 IgG are positive in only 2.5% of cases.[8] Unfortunately, we were not able to examine the CSF for SARS-CoV-2 due to technical difficulties but CSF laboratory findings supposed viral etiology.

Brain abnormalities can be visualized in 50% of cases through neuroimaging.[2] According to another study, radiological features are detected by CT in 37% and by MRI in 81.5%. The hyperintense lesions are visualized mainly in the white matter, temporal lobe, or corpus callosum. Approximately 39%–50% of encephalitis patients have no radiologic features for brain damage.[2,6]

There is no specific treatment for encephalitis caused by SARS-CoV-2. Acyclovir treatment is often initiated due to the suspicion of HSV etiology. Acyclovir administration can be discontinued when this possibility is ruled out.[9] We used the same therapeutic approach for our patient. Therapeutic effects have been observed after corticosteroid treatment (dexamethazone, methylprednisolone), I.V. immunoglobulin, plasmapheresis, monoclonal antibodies (tocilizumab, rituximab) according to reports and case series in the literature.[9]

The differential diagnosis between encephalitis and encephalopathy in COVID-19 patients is important. Both conditions may occur with similar clinical presentation. Encephalopathy is significantly more common and is characterized by diffuse cerebral dysfunction manifested by altered mental status ranging from confusion, delirium to coma. Encephalopathy can be a result of acute respiratory, renal, hepatic or cardiac failure, coagulopathy, sepsis, shock, dyselectrolytemia, and multiorgan dysfunction in critically ill patients.[10] In the majority of patients with encephalopathy, CSF was reported as normal.[11]

Patients with encephalitis generally need ICU care and occasionally mechanical ventilation. Our patient was intubated and mechanically ventilated for several days because of severe seizures and an apneic episode, not because of pulmonary damage or other organ dysfunction.

By definition, SARS-CoV-2-associated encephalitis is an inflammatory process with CSF pleocytosis and elevated protein in COVID-19 patients. Definitive evidence for direct neuroinvasiveness could include RNA PCR positive tests and SARS-CoV-2-specific antibodies in CSF. Although an increasing number of cases of SARS-associated encephalitis have been reported, few (25%) actually meet the strict criteria for direct SARS-CoV-2-associated encephalitis.[6,11]

CONCLUSION

Our clinical case confirms the clinical variety of COVID-19 and the possibility of severe neurological manifestations. Encephalitis is rare but potentially life-threatening condition due to cerebral edema, seizures and focal neurological signs. Physicians should be aware of encephalitis in SARS-CoV-2 patients with neurological symptoms.

Author contributions

P.A. was responsible for the conceptualization and the original draft writing; Y.K. was involved in the microbiological evaluation and interpretation; P.A., A.T., and S.Z. were responsible for the patient's treatment; M.S. was responsible for supervision. All authors contributed to the reviewing and editing of the manuscript.

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Competing Interests

The authors have declared that no competing interests exist.

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Энцефалит, связанный с SARS-CoV-2: отчёт о клиническом случае

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Резюме

COVID-19 в большинстве случаев проявляется респираторными симптомами и признаками. Центральная нервная система может быть поражена напрямую или косвенно, что подтверждается рядом неврологических отклонений и осложнений. Целью данного исследования является представление клинического случая энцефалита, связанного с SARS-CoV-2, и выявление тяжести этого неврологического заболевания в течение COVID-19. Методы этиологической диагностики включают исследование мазка из носоглотки и спинномозговой жидкости методом PCR.

45-летний мужчина с лихорадкой, изменённым сознанием и тонико-клоническими судорогами был госпитализирован в Клинику инфекционных заболеваний Университетской больницы „Св. Георги“ в Пловдиве. Диагноз энцефалита COVID-19 основан на типичных клинических и лабораторных данных, положительном результате PCR SARS-CoV-2 и исключении других вероятных возбудителей в спинномозговой жидкости. Пациент был выписан через две недели после поступления без неврологических последствий. Случай подтверждает клиническую разновидность COVID-19 и возможность тяжёлых неврологических проявлений. Энцефалит – редкое, но потенциально опасное для жизни состояние. Врачи должны быть информированы об энцефалите у пациентов с SARS-CoV-2 с неврологическими симптомами.

Ключевые слова

центральная нервная система, COVID-19, нейроинфекция, PCR, судороги