



Acute Viral Encephalitis Associated with SARS-CoV-2

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Abstract

Encephalitis is an inflammation of the brain parenchyma caused by either viruses or bacteria. The viruses can broadly cause central nervous system infections. As the viral encephalitis with severe complications can be life-threatening it has raised global concerns. Depending on the pathogen, host immunity and the environment in which patient live, the expansion of brain involvement and prognosis of this disease would be different. Coronaviruses are pathogens that typically involve respiratory and gastrointestinal system. Although rare, the novel coronavirus (COVID-19) can probably involve central nervous system and cause neurological symptoms such as headache, seizure, myopathy and impaired consciousness. The viral neurotropic and neuroinvasive characteristics of some coronaviruses facilitate accessing the nervous system through nasal cavity and cause some neurological disorders like encephalitis, demyelination and neurodegeneration disorders. Here we present two cases that according their history, manifestations and laboratory data confirmed COVID-19 followed fatal viral encephalitis.

Keywords: Coronavirus; COVID-19, Encephalitis; SARS-CoV

Introduction

Human Coronaviruses (H-CoV) are six types including H-CoV 229E, H-CoVNL63, H-CoV-OC43, H-CoV-HKU1, SARS-CoV and MERS-CoV [1]. They are known as respiratory system pathogens involving respiratory mucosa and depending on the host immunity and viral virulence may be widespread and invade the brain, liver, kidneys, eyes and spleen [1]. They may rarely involve CNS and cause encephalitis, demyelination and degeneration [1,2]. According to an animal model research evaluating the neurological effects of coronaviruses on mice and rats the results demonstrated the affinity of MHV (Mouse Hepatitis Virus) to different organs including CNS [1]. They found this virus is hepatic-neurotropic and can cause different diseases from hepatitis to encephalitis and chronic demyelination diseases such as multiple sclerosis [1,3]. The most common characteristics of MHV is being hepatotropic-neurotropic. MHV-A59 is hepatotropic-neurotropic and MHV-3 is hepatotropic [1]. Viral infection caused by MHV-JHM or MHV-A59 occurs intranasally (olfactory bulb) or intracranially [1,4]. SARS-CoV is a neuroinvasive virus and spreads to the brain through olfactory bulbs and infects neurons by inhibiting the infiltration of the immune system, it causes the death of the host [4,5].

MHV is a member of *coronaviridae* and one type of beta coronavirus. Its genome is about 32 kilobases and has 4 proteins in its structure: Spike (S), Envelope (E), Membrane (M) and Nucleocapsid (N). Some types have just two proteins Hemagglutinin-Esterase (HE) and Internal Protein (I). Some reports declared that pathogenesis of this virus depends on simultaneous activation of protein M, E and N [1]. Virus by using its s-glycoprotein binds with the target cells and the complex of virus-cell membrane facilitates entering and distributing the virus [1,6,7]. CNS involvement differs in the speed of distribution in the brain. The faster virus enters the wider it stimulates the host immune system. This process results in lymphocytic invasion to CNS and significantly increases the CD4+ and CD8+ T-cells [1]. Nucleocapsid protein (N), predominantly affects transition the virus. It increases not only the virus entering ability through axonal route but also interneuron distribution [1]. Among all human coronaviruses, there are 5 types involving H-CoV-OC43, HCoV-229E causing neural cell infection and remain in the human brain [3,4,6,7]. At present our knowledge on the coronavirus and the mechanism involving CNS is not considerable. Therefore, it is reasonable considering patients have severe respiratory symptoms associated with neurological symptoms such as headache, seizure and altered level of consciousness at the same time as the viral encephalitis of human coronavirus. Since the information about human coronavirus is not available that much, it is expected that its morbidity and mortality rate are more than other pathogens. Hence, we need lots of diagnostic

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Figure 1: CXR showing multifocal patchy consolidation.



Figure 2: Chest CT-scan showing: Showing patchy consolidation and nodule.

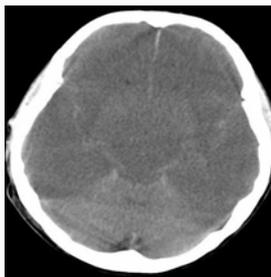


Figure 3: Brain CT-scan, showing diffuse brain edema. Third, fourth and lateral ventricles are invisible.

workups and effective treatment to improve prognosis. According to this point that some types of non-human coronaviruses are neurotropic and can directly damage CNS, one of the diagnostic keys is probably virus nucleic acid evaluation of CSF through RT-PCR [8]. Meanwhile the assessment of antiviral intrathecal antibody synthesis will be utilized indicating viral invasion to CNS [8]. Moreover, based on some studies, Angiotensin Converting Enzyme 2 (ACE-2) has known as the SARS-CoV2 functional receptor [8]. This receptor has seen in different organs such as CNS, and musculoskeletal system and seems to be related to neurological signs and symptoms happening directly as well as indirectly in both CNS and musculoskeletal [8].

Case Series

Case 1

First patient was a 49 y/o lawyer man without any past medical history and drug history. He suffered from fever, headache, productive cough and sneeze two days prior he referred. He had tonic-clonic seizure three times every 30 min. After the last seizure, the disorientation to place, time and persons happened. He referred to our hospital and admitted. After admission, respiratory distress and decrease of consciousness level happened therefore; he was intubated and transferred to ICU. In physical examination his temperature was 38/3 axillary. Although initially he could obey

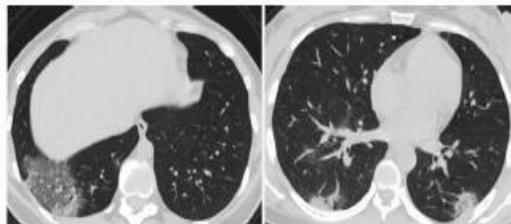


Figure 4: Chest CT-scan: Showing bilateral patchy pure ground glass opacities.

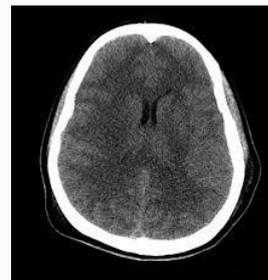


Figure 5: Brain CT- scan: Absence of sulcal markings and partial poor differentiation of white and gray matter from diffuse bilateral cerebral hemispheric edema.

some orders, the level of consciousness progressively decreased. The laboratory data showed leukocytosis 17600 with lymphopenia 4/3%, high level of CPK (919) and LDH (2336). In the brain CT scan diffuse brain parenchymal edema was seen and the lateral ventricles as well as third ventricle were partially invisible. Chest X-ray showed multifocal patchy consolidation. CSF analysis findings were high level of protein up to 70 mg/dl, glucose 30 mg/dl, WBC 11. The other data were normal. Due to lack of knowledge about coronavirus outbreak, Reverse Transcription Polymerase chain (RT-PCR) was not done but CSF-PCR was not performed on. Patient expired after 13 days (Figure 1-3).

Case 2

A 39 y/o single man working in a hypermarket referred to our hospital after five days of fever, trembling, dry cough and myalgia followed respiratory distress and chest discomfort. He admitted in the emergency ward. In physical examination he was febrile with temperature of 39°C orally and diffuses crackle heard in chest auscultation. On the third day, patient got disoriented, agitated and suffered from headache. After a long episode of tonic seizure, the level of consciousness decreased therefore, patient immediately transferred to ICU and ventilated. Seizures continued but after injecting the appropriate antiepileptic agents for status epilepticus, they stopped. Pupil's examination showed anisocoria. He didn't response to either verbal or painful commands. Complete blood cell count showed leukocytosis (WBC: 19,760), with lymphopenia 3/7%. In serum chemistry, ALT: 49, AST: 54. The level of CPK and LDH significantly elevated. These values were 1,003 and 3,119 respectively. CSF analysis revealed glucose level of 33 mg/dl, protein level of 74 mg/dl, WBC of 9 and RBC count of 2. CSF culture was negative. PCR for COVID-19 was positive. Due to his poor condition MRI was not performed. The second day that he transferred to ICU, he died (Figure 4,5).

Conclusion

Considering the COVID-19 signs and symptoms are quite

various and moreover encephalitis is a potentially fatal complication of viral infection therefore, it is so important for all doctors to be aware of these diseases and consider the symptoms like headache, loss of consciousness, seizure as probable encephalitis to immediate diagnosis, treatment and even prevention of any sequels.

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