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Response to "SARS-CoV-2 related encephalitis requires documentation of the virus in the cerebrospinal fluid"

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Dear Editor,

We appreciate your interest in our report[1] and your insightful comments. We would also like to thank you for the opportunity to respond to the issues addressed in your letter and to clarify aspects of our audit in relation to these concerns.

If we start with the laboratory results, the patient had normal laboratory values except for the positive viral PCR at current admission. All laboratory data were provided when the publication was first submitted but during revision it was advised that values within normal range were not necessary. The diagnosis of COVID-19 at the second admission was removed by mistake and an erratum has also been published.[2]

The patient's laboratory and reference values upon admission were as follows: pH: 7.39 (7.35-7.45); partial pressure of carbon dioxide (pCO_2): 34 (35-45) mmHg; O_2 saturation: 80%; bicarbonate (HCO_3): 21 mmol/L; fasting blood glucose (FBG): 128 (70-100) mg/dL; creatinine: 0.66 (0.7-1.1) mg/dL; ferritin: 12 (11-190) ng/mL, triglyceride: 34 (40-150) mg/dL, procalcitonın: 0.04 ng/mL, CK-MB: 0.6 (0-5.2) IU/L, D-Dimer:0.19 (0-0.55) ng/mL, Troponin I: 1.1 (0-34.2) ng/mL , Na: 142 mEq/L; K: 4.2 mEq/L; Mg: 1.9 mEq/L; Ca: 8.1 mg/dL; phosphorus: 3 mg/dL; aspartate aminotransferase (AST): 14 U/L; alanine aminotransferase (ALT): 29 IU/L ; white blood cell count (WBC): 15,540 (4,100-10,500)/μL; lymphocytes: 7.8%; Hemoglobin (Hb): 12.7 (11.8-16.5) g/dL; platelet count: 256,000 (145,000-400,000)/μL; albumin: 5.0 g/L, and C-reactive protein (CRP)= 0.1 mg/L, COVID-19 (SARS-CoV-2) reverse transcriptase PCR: positive, brain natriuretic peptide (BNP): 10 (0-100) pg/mL. On the third day of admission, D-dimer (1.14 mg/L), Troponin I (150 pg/mL), and BNP (38.2 pg/mL) increased .

The patient had a history of a COVID-19 infection five months ago. This was his second infection with COVID-19. We assume that the present COVID-19 infection caused the neurological damage, but the quick decline may have been brought on by the previous SARS-CoV-2 infection he had five months prior. It is possible for the adaptive immune system to become engaged, which would stimulate immunological memory and cause significant central nervous system (CNS) damage. The patient was diagnosed with encephalitis due to the clinical presentation and cerebral magnetic resonance imaging (MRI) which showed cytotoxic edema in the fronto-temporo-parietal regions bilaterally. As we previously indicated, our patient initially displayed neurological symptoms such as headache, dizziness, and finally loss of consciousness. He did not exhibit severe respiratory symptoms at this time. We also agree with you that a limitation was that no other viral or causal agents were ruled. This was because our of laboratory insufficiencies. At the time this patient was admitted the national vaccination program for children in Turkey had not yet introduced the COVID-19 vaccine.

Although there is not a widespread agreement, an autopsy may be done when a death is suspicious or when there is a suspicion that an

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unidentified infectious agent, a condition that has not been properly diagnosed, or another factor caused the death. In our setting, an autopsy was not a recommended as the death was brought on by COVID-19.

In spite of the fact that virus isolation is necessary for a certain diagnosis of viral encephalitis, COVID-19 is a challenge because SARS-CoV-2 transmission is transient and the CSF titer may be extremely low or even negative in some cases.[3,4]

Cytotoxic edema is characterized by intracellular fluid accumulation that results in cell swelling. Minutes after acute CNS trauma, cytotoxic edema, also known as cellular swelling, becomes apparent. Following cytotoxic edema, ionic edema, an extracellular edema that develops in the presence of an intact blood brain barrier, emerges. Along with acute ischemic stroke, traumatic brain injury, subarachnoid hemorrhage, fulminant liver failure, global ischemia, infections (encephalitis, menegitis, or abscess), and postsurgical edema are other conditions that can cause cytotoxic edema. Vasogenic edema may also be brought on by these situations.[5] After the patient was intubated, his health and the imaging equipment were not good enough for an MR venogram.

One of the tests performed in patients to find thrombosis is a D-dimer level. D-dimer and fibrinogen concentrations have been seen to rise in the early stages of COVID-19 disease, according to studies. D-dimer levels that increase by 3 to 4 fold are associated with a poor prognosis. When COVID-19 infection is in its first stages, fibrinogen and D-dimer levels usually rise. These individuals' elevated D-dimer levels may be brought on by thrombin production-inducing endothelial cell malfunction or inflammatory reactions to COVID-19 infection.[6] In our patient, D-dimer started out normal, but on the third day of hospitalization, it had increased six times. The 6-fold increase in our patient's D-dimer might have contributed to the disastrous outcome since a D-dimer increase of 3–4 fold is linked to a poor prognosis.[6]

Encephalitis in children has a wide range of potential diagnoses, and etiology examination is frequently inconclusive. A developing cause of non-infective encephalitis with a wide range of symptoms is autoimmune encephalitis (AE). The traditional method for diagnosing AE is the finding of antibodies in a patient who has a clinical profile suggestive of the disease. Children with autoimmune encephalitis typically present with a variety of subacute symptoms. The appearance of oligoclonal bands, lymphocytic pleocytosis, and increased protein levels in the cerebrospinal fluid (CSF), among other concurrent inflammatory signs, may be present but are often nonspecific. Particularly on fluid-attenuated inversion recovery (FLAIR) or T2-weighted images, MRI of the CNS may potentially reveal anomalies that offer diagnostic hints.[7,8] It was reasonable for us to treat the patient as having acute encephalitis in light of the patient's clinical deterioration and ongoing COVID-19 infection. Findings from the radiology and clinical fields did not support an autoimmune encephalitis.

When the patient was admitted, the brain scan results were normal. After six hours of admission, he experienced status epilepticus. A non-enhanced CT we acquired showed cortical sulci effacement, which is brain edema. A pressure differential between the supratentorial and infratentorial compartments is supported by the available data. Elevated pressure both above and below the tentorium cerebelli may contribute to the development of such a pressure gradient.[9] In these conditions, a lumbar puncture might have resulted in bilateral uncal herniation.

The authors questioned how the D-dimer increased on the 3rd day if the patient died 48 hours after admission but this was when brain death occurred. The patient passed away on the eighth day of admission. The expected laboratory finding of D-dimer increase in COVID-19 infection is significant for prognosis.[6]

To fully comprehend SARS-CoV-2's neurologic involvement, more cases are required. We

attempted to make patient-specific decisions and schedule the course of the treatment in accordance with the clinical course. Considering the patient's COVID-19-related acute encephalitis, especially given the positive COVID PCR on the day of arrival, was a consideration. We did not take AE into account. In reality, the recommendations for the diagnosis of AE advise performing a full antibody panel in a case of suspected AE, which includes antibodies against intracellular, surface antigens, and ion channels. The overlap in diagnostic and therapeutic aspects has grown so large in recent years as our understanding of this disease has increased that the antibody-based diagnosis has gradually given way to a diagnosis primarily based on clinical symptomatology.[8]

We believe that this case report will emphasize the deteriorating prognosis of acute COVID-19 encephalitis with an elevated D-dimer. Initial findings from the diffusion-weighted series may be apparent on brain MRI. The other MRI series could be normal. To rule out any further sources of neuronal injury, we advise using MRI with diffusion-weighted images early on in the neurologic problem.

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