COVID-19 Encephalopathy with Severe Neurological Symptoms: A Clinical Case Presentation with Literature Review

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INTRODUCTION

In December 2019, the first cases of a new coronavirus infection were reported in the Chinese city of Wuhan [1], and on March 11, 2020, the World Health Organization declared the outbreak of this novel SARS-CoV-2 virus a global pandemic [2]. The manifestations of COVID-19 in-
fection are of an extremely wide spectrum, ranging from asymptomatic to acute respiratory, renal or other organ failure. The most common symptoms are fever, cough, shortness of breath, headache and muscle aches, nausea, abdominal pain, and diarrhea [3]. It is estimated that approximately 50% of patients with COVID-19 infection may have neurological symptoms [4]. One of the notable neurological complications is encephalopathy. Acute encephalopathy is a non-specific term used to describe an acute disorder of the brain that occurs clinically as a change in the level of consciousness [5]. Most recent studies have shown that up to 36% of hospitalized patients with COVID-19 experience encephalopathy symptoms such as confusion, delirium, or somnolence [6]. Some patients may experience additional symptoms such as cognitive or memory impairment, convulsions, headaches, incoordination, or myoclonias [4, 6]. The pathogenesis of COVID-19 encephalopathy may be multifactorial. Currently, most of the data suggest hypoxic, metabolic damage caused by the cytokine storm as well as characteristics of the virus’s own neurotropism.

In this article, we present a rare clinical case in which a young patient diagnosed with COVID-19 infection with mild primary respiratory symptoms progressed and developed new neurological symptoms. COVID-19 encephalopathy was diagnosed after a detailed examination and exclusion of other possible causes.

CASE REPORT

On May 12, 2021, a 37-year-old man arrived at the emergency unit for infectious diseases complaining of double vision, dizziness, impaired gait and memory; the person could not remember the day’s events or the exact date. The patient’s anamnesis showed that on May 2, 2021, he was determined as COVID-19 positive. At that time, blood tests showed a moderate increase in C-reactive protein (16.5 mg/L) and pulmonary radiography revealed bilateral viral pneumonia but with a stable course, so the patient was treated and isolated at home. The patient had primary arterial hypertension, irregularly used antihypertensive drugs, and had no other chronic conditions. There was no alcohol or drug use, no tick bites were observed. On May 8, new symptoms appeared – double vision, memory impairment, the patient did not feel like himself, it became difficult to walk and talk. On May 12, the patient felt a further worsening of his overall condition and therefore sought medical attention.

In the emergency unit, the patient’s blood tests showed elevated cytolytic liver enzymes (ALT 127 U/L), while other tests were within normal range. The patient was examined by a neurologist, he was partially oriented in place and time (did not know the exact date, nor events of the day, nor where he arrived), showed signs of dysarthric speech, and had double vision. No obvious paresis and sensory disturbances were observed, but during the Romberg test, the patient was unstable, his gait was ataxic, he spread his legs wide when walking, and could not walk without assistance or perform limb coordination tests accurately. No acute abnormalities were observed after urgent head computed tomography (CT). The patient was hospitalized for a more detailed examination for acute focal neurological symptoms. During hospitalization, the patient underwent a lumbar puncture, his cerebrospinal fluid (CSF) was examined (leukocytes 6/µL, protein 0.526 g/L) and head magnetic resonance imaging (MRI) with MRI angiography was performed. The obtained images were
evaluated for the possibility of diffuse changes in the white matter (Fig. 1), it was recommended to repeat the visual examination, but no significant changes were found after repeated imaging.

To exclude a possible autoimmune process, mosaic studies of autoimmune encephalitis were performed with a negative result. Anti-neuronal antibodies were tested, positive (++) non-specific anti-amphiphysin was detected, other antibodies were negative. Antibodies to HIV and tick-borne encephalitis were also negative. During inpatient treatment, the patient underwent repeated electroencephalography (EEG) – the findings suggested general changes in bioelectrical activity (possibly encephalopathic) with unstable lateralization in both the left and right frontal-temporal areas, regular alpha activity, recurrent synchronized intermittent theta-delta activity; epileptiform activity was not recorded (Fig. 2).

Due to the persistent disorientation and emotional lability, the patient was consulted by a psychiatrist, however, mental disorders were considered to be secondary, caused by a neurological disease. After a detailed examination of the patient, an interdisciplinary medical concilium was held which concluded that the diagnosis of COVID-19 encephalopathy was confirmed by excluding ischemic, autoimmune, and toxic encephalopathies. Since there is no specific treatment for this disease, the patient was given symptomatic treatment. After the course of treatment, the patient’s condition improved – memory impairment regressed, coordination improved. The patient could walk with the help of walking aids, however, during the Romberg test, he remained unstable, anxiety and decreased physical capacity were also observed. In the absence of biopsychosocial function, the patient continued rehabilitation treatment after which he became fully mobile and was discharged home with a Barthel score of 95 and MMSE score of 30.

In the next section, we will discuss possible theories of the pathogenesis of COVID-19 encephalopathy, clinical manifestations, recommended diagnostic tests and interpretation of findings, treatment options, and disease prognosis.

**PATHOGENESIS**

The pathogenesis of COVID-19 encephalopathy may be multifactorial. Neurological complications are thought to be caused by both the direct effects of the virus to the nervous system and the systemic response of the organism to the infection [7]. The virus is currently known to cause a cytokine storm syndrome which is characterized by high production of anti-inflammatory markers such as tumor necrosis factor alpha (TNF alpha), interleukin-6 (IL-6), and interleukin-1beta (IL-1β) [8]. The systemic inflammatory response can lead to the increased blood-brain barrier permeability, allowing peripheral cytokines to enter the central nervous system (CNS). High levels of circulating anti-inflammatory cytokines can cause a change in the state of consciousness. In addition to the cytokine storm, hypoxia and metabolic disturbances are also caused which disrupt the normal functioning of the brain [9]. Coronavirus has also been shown to have neurotropism through the renin-angiotensin system [10]. The surface of the SARS-CoV-2 virus contains spike proteins the virus uses to bind to angiotensin-converting enzyme 2 (ACE2) receptors in host cells. In humans, ACE2 receptors are found in the cells of various organs, including the nervous system and skeletal muscles, and play an important role in both regulating blood pressure and mechanisms of atherosclerosis. One of the possible mechanisms of neurotropism is the direct spread of the virus through the blood-brain barrier via ACE2 receptors located in the cerebrovascular endothelial cells [11]. By binding to the ACE2 receptors, SARS-CoV-2 virus can damage vascular endothelial cells by impairing mitochondrial function and endothelial nitric oxide synthetase activity, leading to secondary effects on
Table. Possible etiologies of encephalopathy for differential diagnosis according to P. Atluri et al. [13]

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxic encephalopathy</td>
<td>Medicines, narcotics, toxic chemicals (lead, mercury, arsenic)</td>
</tr>
<tr>
<td>Metabolic encephalopathy</td>
<td>Hepatic or renal insufficiency, dehydration, electrolyte imbalance, thiamine deficiency</td>
</tr>
<tr>
<td>Trauma</td>
<td>History of traumatic brain injury, recurrent trauma</td>
</tr>
<tr>
<td>Encephalopathy of infectious origin</td>
<td>Bacterial, viral origin. Prion disease, Lyme disease encephalopathy, Salmonella infection encephalopathy</td>
</tr>
<tr>
<td>Hereditary encephalopathy</td>
<td>Mitochondrial encephalopathy</td>
</tr>
<tr>
<td>Autoimmune encephalopathy</td>
<td>Hashimoto’s encephalopathy</td>
</tr>
<tr>
<td>Systemic encephalopathy</td>
<td>Caused by hypertension or hypotension, hypoxia or epilepsy</td>
</tr>
</tbody>
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the cardiovascular and cerebrovascular systems [7]. Another possible mechanism for SARS-CoV-2 entry into the CNS is through olfactory neurons, given that one of the first signs of damage to the CNS is anosmia [11]. The unique anatomical structure of the olfactory nerves and the olfactory bulb in the nasal cavity and anterior part of the brain becomes a channel between the nasal epithelium and the CNS [12] which may be a direct pathway for the spread of SARS-CoV-2 virus. Post-mortem histological brain samples suggest that there is currently more evidence that CNS damage may be caused by the systemic inflammatory response, ischemic changes due to systemic hypoxia, local vascular endothelial damage or thrombosis and toxic effects of metabolites than by direct exposure to the virus itself [13].

CLINICAL SYMPTOMS

Encephalopathy is more common in patients with severe COVID-19 treated in the intensive care unit. In a study of 509 hospitalized COVID-19 patients, 31.8% were diagnosed with COVID-19 encephalopathy [5]. The study found that encephalopathy is more common in elderly patients. Risk factors for encephalopathy included severe COVID-19, shorter time to onset of symptoms, adjacent neurological disorders, history of chronic disease, male gender, smoking, and obesity [5].

Encephalopathy may also be a major and one of the first symptoms of COVID-19. Of 817 patients diagnosed with COVID-19 infection, 28% had encephalopathy. Among these patients, 16% had a change in consciousness as the main symptom and 37% had no typical symptoms of COVID-19 such as fever or dyspnea [14].

COVID-19 encephalopathy is characterized by diffuse brain dysfunction, usually manifested by changes in the level of consciousness, ranging from confusion and delusional symptoms to somnolence or deep coma [15]. Patients with encephalopathy may also experience adjacent clinical symptoms such as convulsions, headache, extrapyramidal symptoms, or incoordination [7].

It is worth noting that non-specific symptoms such as myalgia, dizziness, anosmia, and dysgeusia may be observed in the early stages of the disease [8]. Based on the analysis by Liotta et al., encephalopathy was found to be the third most commonly observed neurological symptom after myalgia and headache, significantly impairing overall functional outcomes and increasing patient mortality [5].

DIAGNOSIS

Specific abnormalities are often not found in laboratory or imaging tests in patients with COVID-19 encephalopathy, however, analysis of recent studies helps to reveal some patterns and models of changes in tests of patients with COVID-19 encephalopathy [7]. Liotta et al. showed that blood tests in patients with COVID-19 encephalopathy showed higher white blood cell count, elevated C-reactive protein, D-dimers, ferritin, and procalcitonin concentration than in patients with COVID-19 infection without encephalopathy. Nevertheless, some other studies do not record statistically significant changes between these groups of patients [16].

In case of suspected encephalopathy, it is recommended to perform a lumbar puncture and CSF examination as well as an EEG and head MRI to exclude other pathologies that could worsen the state of consciousness. Information on differential diagnostics is presented in the Table.

CSF examination findings in patients with COVID-19 encephalopathy are often non-specific. CSF examinations in recent studies have revealed that the majority of patients tested had normal white blood cell count, normal glucose and protein levels and in most cases SARS-CoV-2 virus was not detected by a PCR test. [4]. Patients with elevated white blood cell count in their CSF should be thoroughly investigated for encephalitis and other possible infectious causes [7].

In patients with COVID-19 encephalopathy, EEG abnormalities are often found that correlate with disease severity and pre-existing neurological diseases, including epilepsy. Changes in the activity of the frontal part of the brain are usually found and are considered to be one of the biomarkers of COVID-19 encephalopathy [17].

In the study by Antony and Haneef, diffuse deceleration of brain activity was the most common EEG finding in two-thirds (68.6%) of patients. It has been hypothesized that EEG alterations in the frontal part of the brain are due
to direct viral damage, while diffuse changes may be due to the involvement of a systemic response process [17]. Excess generalized frontal delta waves, three-phase waves, and smaller alpha and beta wave amplitudes are also described [18]. Several studies have shown that for the confirmation of COVID-19 encephalopathy, EEG has demonstrated greater sensitivity compared to head CT scan or MRI. Epileptiform changes were often observed in patients without evidence of changes in visual neurological diagnostic tests [19]. In one study, EEG changes were found in as many as 83% of patients with suspected COVID-19 encephalopathy compared to 59% detected on head MRI [20].

Data on head MRI features associated with COVID-19 encephalopathy are currently lacking. One study reviewed head MRI of 190 patients with severe COVID-19 infection, most of whom had symptoms of encephalopathy. Of these, only 37 patients showed changes that could be associated with acute clinical symptoms of encephalopathy such as medial-temporal signal changes, microhaemorrhages, and multifocal white matter damage seen in diffusion restriction and FLAIR sequences [21]. Another study found that about half of visual neurological diagnostic tests that are performed in people with encephalopathy show acute disorders. The most frequently detected changes are symmetrical multifocal foci of leukoencephalopathy, diffusion restriction changes involving the periventricular and deep white matter, as well as signs of microhaemorrhage and leptomeningitis [22].

**TREATMENT**

There is no specific treatment for COVID-19 encephalopathy, so treatment consists of treating the underlying disease and symptomatic treatment. Due to the fact that patients diagnosed with COVID-19 encephalopathy generally encounter a more acute course of the disease, they are more likely to receive supplemental oxygen therapy and glucocorticoid therapy [23]. Prophylactic antiepileptic therapy should be considered for patients in severe condition, who also experience seizures and impaired consciousness [24]. The role of glucocorticoids or immunomodulatory drugs in the treatment of patients with COVID-19 encephalopathy is not yet fully clear [7]. In the case of a systemic inflammatory response, immunomodulatory therapy with high-dose intravenous corticosteroids (methylprednisolone 500 mg-1 g daily for 5 days) or intravenous immunoglobulins (0.1-0.5 g/kg daily for 5-15 days) is recommended [25, 26]. Replacement plasmapheresis has also been shown to result in a faster improvement in consciousness in some patients. However, glucocorticoids or other immunomodulatory therapies should not be considered a standard treatment option for patients with COVID-19 encephalopathy, as there is still a lack of research to support the efficacy of this treatment [7].

**PROGNOSIS**

Encephalopathy is known to be a risk factor for poor outcome. Recent studies have shown that patients diagnosed with COVID-19 encephalopathy have a larger number of bed-days and worse functional capacity, with one-third of such patients remaining with neurological, mostly cognitive, disorders at the time when the patient is discharged from the hospital [1, 27]. Patients with COVID-19 encephalopathy have a higher 30-day mortality rate than those with COVID-19 without encephalopathy [5]. Although the long-term neurological prognosis of patients with COVID-19 encephalopathy is not yet fully understood, it has been shown that residual symptoms tend to regress in the majority of patients monitored after discharge from the hospital [7].

**CONCLUSIONS**

Although the most commonly reported symptoms of COVID-19 are respiratory symptoms and the damage they cause, a large proportion of patients with COVID-19 may have a variety of neurological clinical symptoms. COVID-19 encephalopathy is common in patients with severe disease progression, but it can also occur as a primary symptom in people of all ages. COVID-19 encephalopathy is a diagnosis of exclusion, therefore, to confirm this pathology, a detailed examination of the patient and exclusion of other diseases are required. There is no specific treatment for the disease, and treatment with glucocorticoids or immunomodulatory therapy is recommended to be individualized depending on the clinical situation. This article describes a clinical case of the patient with COVID-19 encephalopathy. It is important to note that the patient was of young age, had mild initial symptoms of the coronavirus infection, and was being treated at home. The patient also did not have clear risk factors such as comorbidities, immunosuppression, or harmful habits that could have increased the risk of developing COVID-19 encephalopathy. The aim of this article is to reveal that even patients with a mild form of COVID-19 infection may experience symptoms of encephalopathy, therefore, a detailed examination of patients with acute neurological symptoms in COVID-19 infection is required.

**References**

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COVID-19 ENCEFALOPATIJA SU GRUBIA NEUROLOGINĖ SIMPTOMATIKA: KLINIKINIO ATVEJO PRISTATYMAS SU LITERATŪROS APŽVALGA
Santrauka
COVID-19 infekcija pasauliyse sėrėja vis daugiau žmonių, todėl, nuoauget antsigurų, naujų ligų, ir apie galimus klininius ligos pasireiškimo simptomus. Nors SARS-CoV-2 virusas dažniausiai yra susijęs su įvairiose sistemos pažeidimais, pastebėta, kad aptikti pasiekti pacientų, sergančių COVID-19 infekcija, tai, tarp gali pasireikšti ir įvairių neurologinių simptomų, tokių kaip anksmita, disgeuzija, galvos skausmas, mėgėjų ar galvos svagaitas. Encefalopatija yra išskiriama kaip viena sunkiausių SARS-CoV-2 viruso sukelto chorinės ir septynis nerynys skiriasi priklausančių, susijusių su ligos trukme, dieninės neįgalumui ir mirtingumui. Šie įvykiai įvairių šiuos pacientus, kurių kliūkia pasireiškia staigiai susijęs su ligomis po mąsčiai. Tik su šių simptomų atsidarymo pradžios būdu būvusiu sveikiniams suveikti. Šiems įvykiams veiksniams – vynės visūnams, vynėkio lytis, trumpesnis laikas