

SHORT COMMUNICATION

Treatment of COVID-19-induced refractory status epilepticus by tocilizumab

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Abstract

Background and purpose: COVID-19 is a novel infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in which neurological complications have been increasingly recognized. Acute symptomatic epileptic seizures and status epilepticus are frequently reported neurological complications associated with this infection. The nervous system damage caused by SARS-CoV-2 may be mediated by the immune system. Interleukin 6 (IL-6), an important component of the cytokine storm, is directly correlated with the severity of symptoms. Tocilizumab is an inhibitor of IL-6 receptors, which blocks IL-6-mediated signal transduction and is used in the treatment of COVID-19 and status epilepticus.

Case report: A patient with the Unverricht-Lundborg disease is presented who had developed refractory recurrent status epilepticus during COVID-19 infection, which was finally controlled by treatment with tocilizumab.

Discussion: Tocilizumab, an IL-6 inhibitor, may be considered as a treatment option in patients with status epilepticus and refractory seizures.

KEYWORDS

COVID-19 infection, status epilepticus, tocilizumab, Unverricht-Lundborg disease

INTRODUCTION

COVID-19 is a novel infectious disease that is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus has become an important cause of pandemics that cause significant mortality and morbidity throughout the world. The presentation of COVID-19 can range from asymptomatic to severe respiratory distress. Studies have reported that approximately 36.4% of COVID-19 patients develop some type of neurological complication [1]. Cases of status epilepticus (SE) associated with COVID-19 infection have been reported in the literature [2, 3]. Although the mechanism of action is not known, these seizures may follow an immunological mechanism called a cytokine storm. New-onset seizures or seizures in epilepsy patients may be triggered by the release of proinflammatory cytokines, especially interleukin 6 (IL-6). This report describes a case with refractory seizures and possible immunological reactions

due to COVID-19 infection, whose condition improved following treatment with tocilizumab.

CASE REPORT

A 21-year-old male patient with a genetically verified diagnosis of Unverricht-Lundborg disease since the age of 10 was admitted to the emergency department due to recurrent seizures. The seizures were rare (one to two times every 3 months) before he got infected with SARS-CoV-2 and was treated with favipiravir 2 months ago. Although the infection was mild with symptoms such as mild fever and cough, it was accompanied by generalized convulsive SE. The patient's seizures continued despite the polymerase chain reaction test for COVID-19 turning negative after a week. Before he had COVID-19 infection, the patient had not experienced SE. However,

in the 2 months after COVID-19, he was admitted to the intensive care unit (ICU) five times and continued to have frequent seizures at home despite being treated with several anti-seizure medications (ASM) (levetiracetam 2000mg/day, topiramate 100mg/day, valproic acid 1000mg/day and clobazam 20mg/day). Cranial magnetic resonance imaging and the vital signs (fever, pulse and blood pressure) were within normal limits. Analyses of the blood and cerebrospinal fluid revealed normal protein and glucose levels without any cells, as well as the absence of other viruses (adenovirus, EBV, CMV, HSV-1, HSV-2, VZV, HHV-6, HHV-7, enterovirus and parvovirus B19) and autoimmune antibodies (extracellular, NMDA-R, AMPA-R1, AMPA-R2, CASPR2, LGI1, GABA-R; intracellular, anti-GAD, anti-Hu, Yo, Ri, Tr, PCA-2, Ma, CV2-1, ANNA-3, amphiphysin antibodies). Except for seizures, the patient did not have any signs of systemic disease caused by COVID-19.

Seizures were partially controlled during treatment with intravenous (IV) corticosteroid (500mg/day) for 9 days followed by IV immunoglobulin (IVIg) 0.4 g/kg/day for 5 days. However, they recurred gradually within a few days and the patient was referred to the ICU again, where the seizures were suppressed by IV infusion of midazolam. However, the patient's seizures resumed when midazolam treatment was discontinued. At this point, considering the stable condition of the patient before infection with COVID-19, tocilizumab (an IL-6 inhibitor) was administered. The level of IL-6 in the blood was as high as 26.9 pg/ml (normal ≤ 5 pg/ml). Tocilizumab was started intravenously at a dose of 4 mg/kg in two cycles, with a total of 800mg, with an interval of 2 days. After the administration of the drug the seizures were immediately controlled, and the patient was discharged from the ICU after 3 days without any seizures. The level of IL-6 returned to normal values at 4.2 pg/ml 2 months after discharge from the hospital, and no seizure was observed during the 6-month follow-up of the patient. In the long-term follow-up of the patient, no drug-related side effects occurred.

DISCUSSION

The COVID-19 virus emerged in Wuhan, China, in December 2019 and caused a global pandemic that affected the entire world. It causes serious complications such as severe acute respiratory tract failure and multiorgan failure from simple respiratory tract diseases and results in death. Anosmia, stroke, central nervous system infection, cranial nerve deficits, encephalopathy, delirium, neuromuscular disorders and seizures are some of the neurological complications in patients infected with SARS-CoV-2 [4, 5]. The various hypotheses for the involvement of the central nervous system include direct infection injury, blood circulation pathway, neuronal pathway (neurotropic virus), hypoxia, immune-regulated injury and angiotensin-converting enzyme 2 [1].

Acute symptomatic epileptic seizures and SE are among the most reported neurological conditions that are associated with SARS-CoV-2 infection. SE not only may induce new-onset seizures

or acute symptomatic seizures but also can exacerbate the pre-existing seizures in patients with epilepsy [6]. Patients infected with COVID-19 may develop new-onset seizures due to hypoxia, metabolic disorders, organ failure, neuro-invasion, cytokine storm or brain damage. A systemic inflammatory syndrome due to cytokine release possibly plays a crucial role in COVID-19-associated SE [3]. Even after the resolution of infection, SE may occur due to the release of proinflammatory cytokines [2]. Moreover, immunotherapy besides ASMs is often required in cases with autoimmune encephalitis [7].

Cytokines released during cytokine storms cross the blood-brain barrier and cause neuroinflammation [8]. In particular, in severe COVID-19 patients, cytokine storms can cause neuronal damage. Cytokines released during a cytokine storm include interleukins such as IL-6 and IL-1 β , granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor (GM-CSF) and tumor necrosis factor. The release of proinflammatory cytokines, including IL-6, is among the main reasons for mortality associated with the disease [9]. CD4+ T lymphocytes are rapidly activated and differentiated into T helper cells and generate GM-CSF. The cytokine environment provides inflammatory monocytes, along with a high production of inflammatory cytokines such as IL-6. As a result, adjunctive therapy with either IL-6 receptor antagonists or IL-6 antagonists has been proposed as a treatment for severe COVID-19 cases. Serum IL-6 levels are significantly elevated in severe COVID-19 disease. A meta-analysis has indicated that such increased levels are significantly associated with unfavorable clinical outcomes, including ICU admissions, acute respiratory distress syndrome and death.

Tocilizumab (a human form of anti-IL-6 receptor antibody), which was originally used for the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis, has recently been suggested for the treatment of severe COVID-19 [9]. Tocilizumab selectively and competitively binds to soluble IL-6 receptors and subsequently blocks the IL-6 signaling, which inhibits the IL-6 receptors that lead to a cytokine storm. Tocilizumab can be applied as first-line therapy to inhibit cytokine release, especially in severe COVID-19 cases [9]. Treatment with tocilizumab has been reported previously, especially in cases of new-onset refractory SE [10], and has been demonstrated to be useful in the treatment of resistant autoimmune encephalitis [11].

Although the seizures of our patient with Unverricht-Lundborg disease (a mild form of progressive myoclonic epilepsy) stabilized following ASM therapy, he developed refractory seizures that evolved to SE after infection with SARS-CoV-19, which resulted in several ICU admissions. Considering that the impairment was due to a possible autoimmune reaction, IV methylprednisolone and IVIg treatment were tried without success. The detection of high IL-6 levels, which were checked to confirm the occurrence of a cytokine storm, encouraged us to initiate tocilizumab treatment. This treatment yielded a favorable response, and eventually the seizures were controlled, along with normalized levels of IL-6.

This patient is an example of an unexpected outcome after COVID-19 where, although the polymerase chain reaction test turned negative within a week, seizures ensued for 2 months until tocilizumab treatment was initiated. This indicated that COVID-19 could cause prolonged immune side-effects. This was associated with high levels of IL-6. The seizure response and normalization of IL-6 levels after tocilizumab treatment emphasized that the seizures were caused by the cytokine storm following the infection.

CONCLUSION

Interleukin 6, an important component of the cytokine storm, is directly correlated with the severity of COVID-19 symptoms, and the possibility of underlying immunological events should be considered in patients with seizures during COVID-19. Therefore, tocilizumab, an IL-6 inhibitor, may be considered as a treatment option in patients with SE and refractory seizures after ASM therapy.

AUTHOR CONTRIBUTIONS

esra koçhan kızilkılıç: Conceptualization (equal); data curation (equal); formal analysis (equal); supervision (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Rumeysa unkun:** Data curation (equal); investigation (equal). **Ugur Uygungoglu:** Conceptualization (equal); project administration (equal). **Sakir Delil:** Funding acquisition (equal); investigation (equal). **Cigdem Ozkara:** Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); supervision (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

WRITTEN INFORMED CONSENT FOR PUBLICATION OF CASE

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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