



Excellent Prognosis in Two Patients with COVID-19 Presenting with Seizures and Encephalopathy

Nöbet ve Ensefalopati ile Başvuran İki COVID-19 Hastasında Mükemmel Prognoz

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Dear editor,

In May 2020, a previously healthy 19-year-old male patient was admitted to the emergency clinic with a generalized onset tonic-clonic seizure (GTCS). Although the nasopharyngeal swab reverse transcription polymerase chain reaction (rt-PCR) for coronavirus disease-2019 (COVID-19) showed a negative result, the thorax computed tomography (CT) results were consistent with COVID-19 pneumonia. The patient received hydroxychloroquine and favipiravir, and a neurological examination was performed upon the patient's arrival, revealing lethargy, loss of cooperation, and disorientation. Contrast-enhanced brain magnetic resonance imaging (MRI) showed leptomeningeal enhancement and marked dural thickening (Figure 1a). The cerebrospinal fluid (CSF) biochemistry and cytological examination results were normal, and the COVID-19 rt-PCR was negative. The patient was started on broad-spectrum antibiotic therapy, as meningitis/encephalitis could not be ruled out, and the detailed laboratory studies excluded other infectious, toxic, metabolic, limbic, rheumatological, and lymphoproliferative etiologies. Due to ongoing seizures, treatment with levetiracetam, lacosamide, and clonazepam was initiated; portable electroencephalography (EEG) could not be performed in the intensive care unit due to contamination concerns. On the seventh day of admission, the control MRI revealed partial regression of leptomeningeal enhancement. Before the patient was discharged from the hospital, he was seizure-free and had a normal neurological examination and EEG results. A brain MRI conducted one month after discharge showed a complete resolution of leptomeningeal enhancement (Figure 1b). After 23 months of

follow-up, there has to date been no recurrence of seizures under levetiracetam treatment.

The second patient was an otherwise healthy 22-year-old male admitted to the clinic with generalized myalgia and a headache in October 2020. The COVID-19 rt-PCR obtained via a nasopharyngeal swab showed a positive result, and the thorax CT results were consistent with a diagnosis of COVID-19 pneumonia. Hydroxychloroquine and favipiravir were used once, and the treatment was discontinued due to nausea. Two days later, the patient presented with altered consciousness and decreased verbal output; he then experienced a GTCS and was admitted to our center. He had a fever, was obtunded, and unable to cooperate. He also presented with mild nuchal rigidity, accompanied by tonic contractions of the extremities. The patient was administered intravenous diazepam, followed by levetiracetam. The results of a cranial MRI showed a slight contrast enhancement in leptomeningeal structures (Figure 1c). Furthermore, the CSF protein level was increased (99 mg/dl), while the glucose and cytological levels were normal. The patient received intravenous acyclovir and ceftriaxone, along with oral remdesivir therapy. Meanwhile, no significant diagnostic positivity was found in either the serum or CSF analysis, including the CSF COVID-19 rt-PCR and infectious, toxic, metabolic, and rheumatological tests. Three days later, the patient's fever decreased, and his alertness improved. After completing the remdesivir treatment, the patient was discharged after a normal neurological examination. The results of the EEG performed before discharge were normal. There was no contrast enhancement in the patient's control cranial MRI one month later (Figure 1d). The patient has

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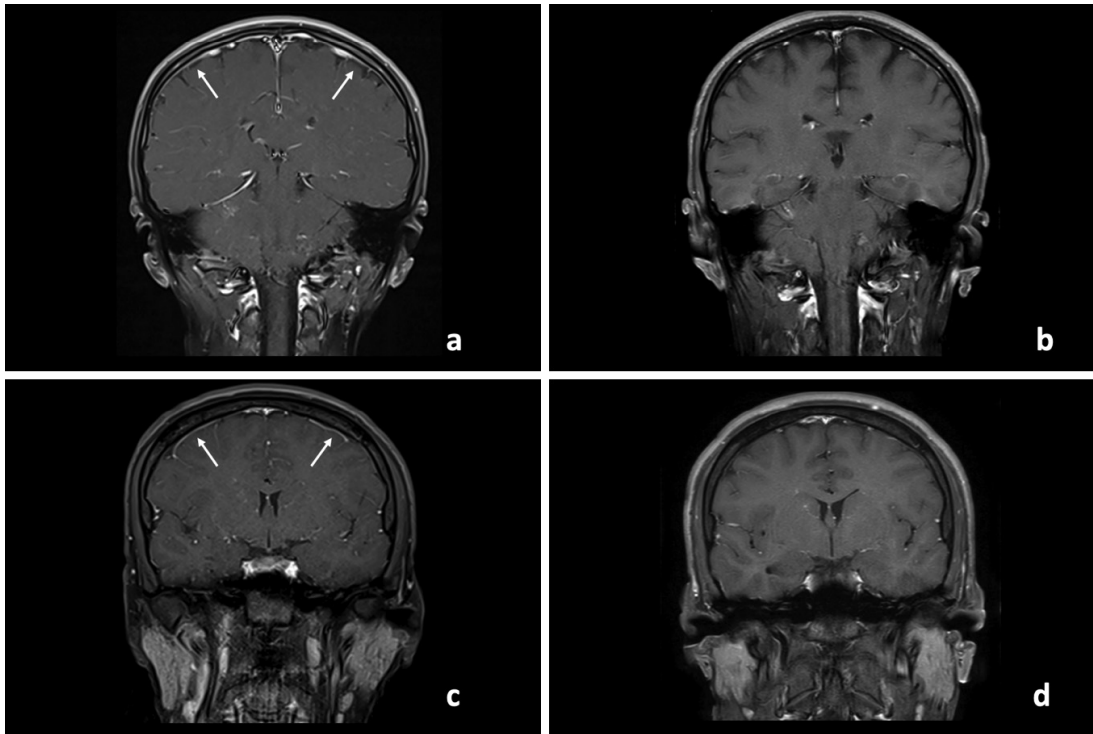


Figure 1. (Upper row): Postcontrast coronal T1W image on admission where (a) shows increased leptomeningeal enhancement and marked dural thickening. Postcontrast coronal T1W image after discharge (b) demonstrates complete resolution of leptomeningeal enhancement. Case 2 (lower row): Postcontrast coronal T1W image on admission (c) shows slight leptomeningeal enhancement. Postcontrast coronal T1W image after discharge (d) reveals complete resolution of contrast enhancement

been followed up at our outpatient clinic for 17 months, and the administration of levetiracetam is being tapered down.

During the COVID-19 pandemic, cases of suspected encephalitis/meningitis have been reported, indicating the possible involvement of COVID-19 in the central nervous system. The frequency of seizures in hospitalized patients with COVID-19 varies in different case series. An earlier multicentric report including 304 patients from China did not observe seizures in any patient (1). Other studies were conducted as follows: (1) March 2020 in Spain (841 COVID-19 patients); (2) between January and June 2020 in the USA (40,469 patients); (3) between February and December 2020 in Iran (5,872 patients). The seizure rates were reported at 0.7%, 0.6%, and 0.8%, respectively (2,3,4). Laboratory investigations have shown that leptomeningeal contrast enhancement is uncommon and that CSF findings, including rt-PCR, may be normal.

The pathophysiology of seizures in patients with COVID-19 can be multifactorial and has led to ongoing discussion in the literature. Acute seizures may occur as a result of other systemic complications of COVID-19 resulting from hypoxia, inflammation, or metabolic disorders (e.g., multi-organ failure, electrolyte abnormalities, and potential drug toxicity) (2). Both above-mentioned patients received hydroxychloroquine treatment, which has been indicated to lower the seizure threshold; however, recent publications have failed to detect substantial evidence that hydroxychloroquine increases seizure risk. On the other hand, the occurrence of new-onset seizures in some patients without a

precipitating factor has led to the hypothesis that infection may be responsible in at least some cases of COVID-19 (2). Currently, numerous reports suggest a negative PCR result in CSF as being a rule rather than an exception (5); this may be due to different reasons, such as variable viral shedding, lower test sensitivity early in the disease, and improper clinical sampling.

Meningitis/meningoencephalitis-related seizures may occur in patients with COVID-19. The rapid and complete improvement of these patients' medical state suggests that a secondary immunological mechanism may be responsible, rather than viral invasion of the CNS. The follow up conducted with the patients suggests that this is a self-limited condition without long-term seizure recurrence.

Ethics

Informed Consent: Patient consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and medical practices: C.A.Ç., D.A., O.S., N.D., Concept: N.D., Design: D.A., N.D., Data collection or processing: C.A.Ç., D.A., O.S., N.D., Analysis or interpretation: C.A.Ç., D.A., O.S., N.D., Literature search: C.A.Ç., N.D., Writing: C.A.Ç., N.D.

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