



COVID-19 in Patients With Seizures and Epilepsy: Interpretation of Relevant Knowledge of Presenting Signs and Symptoms

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Abstract

There are an increasing number of clinical studies for COVID-19, with several large cohort studies documenting initial signs and symptoms. Realizing the need for current information, this summary provides a focused summary of pertinent clinical diagnostic information about neurological involvement of SARS-CoV-2 virus and clinical presentation of COVID-19, especially in relationship to patients with seizures and epilepsy. There is no evidence from cohort studies in the general population that seizures are worsened in COVID-19. However, relative lack of cohort studies in patients with a history of epileptic seizures limit conclusions about effects of COVID-19 patients with epilepsy. Overall, findings indicate seizures and epilepsy are rare, especially in mild COVID-19 cases, but may occur in more severe cases later in the disease course. Caregivers should be vigilant in assessing for possible seizures, especially in patients with systemic effects of severe COVID-19 infections.

Keywords

COVID-19, seizures, epilepsy, signs, symptoms

Introduction

The COVID-19 outbreak continues to evolve, currently with spread throughout the United States, which remains the epicenter of the pandemic. In all areas of medicine, there is a critical need for accurate information to inform an appropriate response to the outbreak. There are an increasing number of clinical studies for COVID-19, but our current understanding in relationship to seizures and epilepsy remains limited by relative lack of cohort studies, especially in patients with preexisting seizures and epilepsy. Realizing both the need for and limitation of current information, this summary provides a focused summary of pertinent clinical diagnostic information about

neurological involvement of SARS-CoV-2 virus and COVID-19, especially in relationship to patients with seizures and epilepsy.

General Issues

There are multiple factors which influence frequency of epileptic seizures, including systemic and environmental factors.¹ COVID-19 therefore may exacerbate epileptic seizures from associated systemic effects not directly related to SARS-CoV-2 virus central nervous system (CNS) infection. Reports of seizures in COVID-19 patients should be interpreted in this context. As detailed below, cohort studies of patients with



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COVID-19 show that neurological complications are relatively uncommon and occur with increased frequency in patients with more severe systemic illness.^{2,3} Lack of early neurological signs and symptoms suggest absence of early direct CNS infection by the SARS-CoV-2 virus. Later neurological manifestations of COVID-19 could be related to either systemic complications of severe infection or direct CNS infection by SARS-CoV-2 virus, which remains uncertain from available data.

Cohort Studies of Clinical Manifestations of COVID-19

Initial Presenting COVID-19 Signs and Symptoms

In a retrospective study of 1099 patients with laboratory-confirmed COVID-19 in China, Guan et al² reported presenting symptoms. The cohort included patients in both the hospital and outpatient setting. There were no reported definitive neurological signs or symptoms on presentation. Additionally, seizures and epilepsy were not listed among coexisting disorders before COVID-19 infection. The reported presenting symptoms of headache (13.6%), fatigue (38.1%), and myalgia or arthralgia (14.9%), theoretically neurologically related, are more typically related to systemic effects of the associated viral infection. Additionally, there were no reported neurological signs. Two subsequently published hospital-based studies reporting initial clinical features COVID-19 showed similar findings, with no definitive presenting neurological signs or symptoms.^{4,5} Focusing on the pediatric population, Dong et al⁶ reported a retrospective nationwide Chinese epidemiological case series of 2135 patients <18 years old with COVID-19. Only 6% of children in the study developed severe or critical disease, in contrast to other comparably designed studies in adult patients showing more severe COVID-19 complications. However, infants (less than 1 year old) and young children (1-5 years old) were at higher risk of a worse clinical course than older pediatric patients. There was no reported incidence of seizures.

Neurological Findings in Severe COVID-19 Infection

In a retrospective case series, Mao et al³ reviewed 214 COVID-19 confirmed hospitalized patients in Wuhan, China, 74 of whom had neurological signs or symptoms. Comparing patients with severe and nonsevere COVID-19 infections as defined by international guidelines for community-acquired pneumonia, patients with severe infection were more likely to have CNS manifestations of disease. Specifically, impaired consciousness and acute stroke were more common in severe cases. There was a single case of epilepsy, in the severe group. Additionally, there was associated hypogeusia and hyposmia in 5.6% and 5.1% of patients, respectively, which showed no difference in occurrence between the severe and nonsevere groups. Muscle injury was reported in 10.7%. In a pediatric study, the International COVID-19 PICU Collaborative⁷

published a cross-sectional study of North American pediatric intensive care units describing the characteristics of 48 critically ill children positive for COVID-19. Two patients had an uncharacterized “neurological” presentation, and 3 patients had seizures as a comorbidity. The intensive care unit (ICU) mortality in this cohort was <5%, significantly lower than adult ICU mortality rates published in other comparable studies.

In the pediatric population, there are a growing number of children who present with a Kawasaki-like disease also known as multisystem inflammatory syndrome in children,^{8,9} which includes persistent fever, single or multi-organ dysfunction, headache, and meningeal signs.¹⁰ Multisystem inflammatory syndrome in children, however, has not been associated with seizures.

Taken as a whole, these studies show initial neurological involvement, especially in mild COVID-19 cases, is rare, but that neurological involvement can occur in more severe cases later in the disease course. Additionally, pediatric patients show less severe COVID-19 manifestations, a finding apparent in initial studies.¹¹ Epilepsy and seizures are a rare complication of COVID-19.

Neurological Findings in COVID-19

Despite findings from studies in the general population, there is great heterogeneity of neurological presentation for individual patients with viral illnesses, so a minority of COVID-19 patients may present with neurological signs and symptoms. SARS-CoV-2 has been reported in the brains from both patients and experimental animals,^{12,13} supporting that clinical manifestations may be related to direct SARS-CoV-2 infection. There are numerous comprehensive reviews of neurological involvement with COVID-19,¹⁴⁻¹⁸ outlining findings of headache, anosmia and ageusia, impaired consciousness, seizures, stroke and vascular events, and peripheral nerve disorders including Guillain-Barré syndrome. In an expert consensus of neurologists from China,¹² COVID-19-related neurological signs and symptoms include stroke, headache, seizures, impaired consciousness, and myalgias. A few patients developed symptoms of neuropathy, for example, paresthesia and bowel/bladder function disturbance. The report stresses that a significant number of patients present without fever, which is confirmed in other studies.¹⁹ Other clinical directives include the importance of treating clinical signs and symptoms appropriately if testing results for SARS-CoV-2 are ambiguous or unavailable, and that some patients had leukopenia before onset of symptoms.

Additional Studies Specifically Aimed at Defining the Relationship Between COVID-19, Seizures, and Epilepsy

Lu et al²⁰ specifically collected data about new-onset acute symptomatic seizures between January and February 2020 at 42 hospitals in the Hubei province, the epicenter of COVID-19 in China. They enrolled 304 patients, none with a prior history

of epilepsy, 108 of whom had severe disease. Patients presented with acute cerebrovascular disease and systemic disorders which could provoke seizures, but without seizures, febrile seizures, or episodes of status epilepticus. Two patients had seizure-like events, diagnosed as seizure mimics due to acute stress reaction and hypocalcemia. The authors concluded that COVID-19 poses minimal risk for acute symptomatic seizures, though a significant portion of severely ill patients had increased potentially provocative risk factors. A limitation of this study was lack of routine or long-term EEG recordings to investigate these seizure-like episodes or to assess for subclinical seizures.

There are studies describing EEG findings for COVID-19 positive patients. Helms et al²¹ reported neurologic features in severe COVID-19 with acute respiratory distress syndrome in 58 patients. Eight patients underwent EEG, all of whom had nonspecific findings with no epileptiform discharges or seizures. Galanopoulou et al²² reported a study of 28 patients under investigation for COVID-19 who underwent hospitalization and EEG studies (either routine or continuous EEG). Of the initial 28 patients, subsequent testing defined COVID-19 positive (n = 22) and negative (n = 6) groups, with respective comparisons of the groups showing indications for EEG testing as new-onset encephalopathy (68.2% vs 33.3%) and seizure-like events (14/22, 63.6%; 2/6, 33.3%). "Seizure-like" events were reported in patients without a prior history of seizures (11/17, 64.7%; 2/6, 33.3%). Intermittent epileptiform discharges, most typically as frontal sharp waves, were present in 40.9% of COVID-19-positive and 16.7% of COVID-19-negative patients. There were no electrographic seizures in either group.

There are now numerous case reports describing seizures and other paroxysmal events in association with COVID-19.²³ Individual reports include a new-onset generalized tonic clonic seizure during likely COVID-19 presentation,²⁴ focal status epilepticus,²⁵ seizures in critically ill patients,²⁶ and COVID-19 presenting with paroxysmal events (possibly seizures) in a 6-week-old male.²⁷

As compared to population-based studies of the initial clinical presentation of COVID-19, studies in patients with seizures and epilepsy are lacking. However, available studies are consistent with the general concept that seizures and epilepsy are infrequently worsened by COVID-19. Case studies, despite their inherent drawbacks in accounting for the multifactorial causes of seizures and epilepsy, highlight that some patients will present with seizures early in the course of COVID-19 infection.

Summary

Multiple reports on COVID-19 show that neurological complications are most associated with severe cases. Individual case reports provide helpful details of acute symptomatic seizures during the clinical course of COVID-19 infection, but overall leave open the question as to whether systemic complications or direct CNS SARS-CoV-2 virus infections cause seizures.

While a neuroinvasive mechanism of SARS-CoV-2 virus CNS infection remains a postulated cause of clinical neurological disease,¹⁶ investigation of new-onset neurological impairments associated with COVID-19 found lack of evidence for direct acute insult of SARS-CoV-19 virus to the CNS.²⁸

There is no conclusive evidence from cohort studies that seizures due to epilepsy are worsened in COVID-19 patients, but there are few cohort studies focusing on patients with a history of seizures and epilepsy. Among the multiple systemic and environmental factors related to COVID-19 infection causing seizures, the underlying susceptibility for seizures due to epilepsy is likely the most significant factor.¹ Therefore, there is a need for further studies evaluating COVID-19 in epilepsy patients. However, clinical experience with seizures and epilepsy in general indicates that exacerbation of seizures, especially from systemic effects such as those caused by severe COVID-19, will be a major concern. Given this likelihood, health care providers should take extra care to assist their patients in preventing potential COVID-19 infection and closely monitor epilepsy patients with COVID-19 for worsening of their seizures.

Declaration of Conflicting Interests

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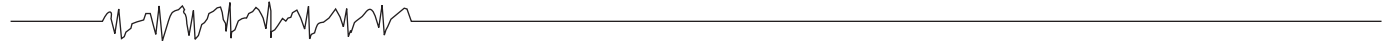
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