COVID-19 Incidence and Death Rate in Epilepsy: Too Early to Tell?

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Incidence and Case Fatality Rate of COVID-19 in Patients With Active Epilepsy

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Objective: This article estimates the incidence and fatality of coronavirus disease 2019 (COVID-19) and identifies potential risk factors for fatality in patients with active epilepsy. Methods: This is a cross-sectional observational study of patients with active epilepsy and COVID-19. A control group was used to compare the cumulative incidence and case fatality rate (CFR). The main outcomes of the study were cumulative incidence, defined as number of patients with active epilepsy and COVID-19 admitted to an emergency department divided by the total number of patients with epilepsy at risk, and CFR based on the number of deaths during the enrollment period. Multiple logistic regression analysis was performed to investigate risk factors for fatality in patients with active epilepsy. Results: Of the 1537 patients who fulfilled the inclusion criteria, 21 (1.3%) had active epilepsy. The cumulative incidence (95% CI) of COVID-19 in patients with epilepsy was higher (1.2% [0.6-2.4]) compared to the population without epilepsy (0.5% [0.5-0.5]). In reverse transcription polymerase chain reaction–positive patients, there were no significant differences in CFR in patients with active epilepsy compared to patients without epilepsy (33.3% vs 8.3%; $P = .266$). Of the 21 patients with active epilepsy, 5 (23%) died. In multivariate analysis, the factor associated with fatality in patients with active epilepsy was hypertension (odds ratio [OR] 2.8 [95% CI: 1.3-21.6]). In another model, age (OR: 1.0 [95% CI: 1.0-1.1]) and epilepsy (OR: 5.1 [95% CI: 1.3-24.0]) were associated with fatality during hospitalization. Conclusion: COVID-19 cumulative incidence was higher in patients with active epilepsy. Epilepsy was associated with fatality during hospitalization. Hypertension was associated with fatality in patients with epilepsy.

Commentary

A novel coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), emerged in December 2019 resulting in a pandemic. The clinical syndrome, coronavirus disease 2019 (COVID-19), has well-recognized pulmonary manifestations, but an expanding literature reports the acute, subacute, and longer term effects on the central and peripheral nervous systems. Persons having the longer term effects are designated to suffer from post-acute sequelae of COVID-19.

Coronaviruses are large, enveloped, RNA viruses separated into 3 genera: alphacoronaviruses, betacoronaviruses, and gammacoronaviruses.[1] These viruses infect humans and typically cause upper or lower respiratory tract, neurological, gastrointestinal, or hepatic disease. There are currently 7 known coronaviruses that can infect humans: of those, 3 (SARS-CoV-2, SARS-CoV1, and Middle East respiratory syndrome coronavirus) are associated with severe disease.[1] Severe acute respiratory syndrome coronavirus-1 (SARS-CoV1) was detected in the cerebrospinal fluid (CSF) using polymerase chain reaction (PCR), and virions were visualized using electron microscopy in neurons in brain tissue specimens, from autopsy donors infected with severe acute respiratory syndrome during the pandemic of 2002 to 2003.[1]

Both SARS-CoV-2 and SARS-CoV1 share a close gene sequence homology and use spike proteins on the viral envelope to bind to mammalian host cells at the angiotensin-converting enzyme 2 receptor. Angiotensin-converting enzyme 2 receptors are found on cells in many organs including the vascular endothelia of the central nervous system.[1] Infection of human brains by SARS-CoV-2 has been suggested in several studies in which viral RNA or protein was detected in the brains and CSF of COVID-19 patients with neurological symptoms.[2,3] Human-induced pluripotent stem cells have been used to generate brain organoids including neural progenitor cells, neurons, astrocytes, oligodendrocytes, and brain microvascular endothelial cells. Experiments in which such brain organoids were exposed to SARS-CoV-2 showed viral infection, degeneration, and death of neurons and astrocytes.[2,3] This suggests that SARS-CoV-2 is neurotropic.

Given the evidence that SARS-CoV-2 can infect neurons and astrocytes, it is possible that the virus could cause seizures and epilepsy in nonepilepsy patients and worsened seizures in persons with epilepsy. Two studies conducted in early 2020 in New York City explored this. In one, the electroencephalograms (EEGs) of patients hospitalized with COVID-19 were examined. Epileptiform patterns were seen in 30% and seizures in 7% of 111 patients undergoing EEG monitoring.[4] In the second, 17.5% of adults with epilepsy reported worsened seizure control.[5] Emotional stress and barriers to care appeared to be substantial contributing factors. Additional research will almost certainly be conducted to determine whether SARS-CoV-2 infection is indeed epileptogenic.

Separate, but important, questions are whether people with epilepsy develop COVID-19, and whether they die from it more often, than people without epilepsy. Cabezudo-Garcia and colleagues[6] aimed to answer this. They studied patients with epilepsy age $\geq$14 years seen in the University of Malaga emergency department between March 13, 2020, and April 12, 2020. Video-EEG and magnetic resonance imaging were conducted as needed. Patients with nonepileptic seizures were excluded. The control group was all patients' age $\geq$14 years without epilepsy. They included patients with acute respiratory infections whose symptoms were consistent with COVID-19. As was common early in the pandemic when testing was not widely available, PCR tests were only done in moderate to severe disease, in mild disease with risk factors, and in all hospitalizations. The authors defined a confirmed case as one with a positive PCR test for SARS-CoV-2, a probable case as one with severe signs or who was hospitalized with clinical examination and X-ray findings consistent with COVID-19 (but not tested with PCR), and a possible case as one having mild symptoms (but not tested with PCR).

The authors defined the cumulative incidence as the number of epilepsy patients seen in the "COVID-19 patient flow" divided by the total number of epilepsy patients in the catchment area served by emergency department. That area contained 302 556 people, and the prevalence of epilepsy in Spain was 0.579%. Those data yielded an estimate of 1751 persons with epilepsy in the catchment area. In the month studied, 1537 patients were seen for possible, probable, and confirmed COVID-19, of whom 21 patients had epilepsy. Based upon the estimated prevalence of epilepsy in the community, the authors calculated that the incidence of COVID-19 in epilepsy patients was significantly higher (1.2%) than in the general population (0.5%). Considering only confirmed cases, the incidence of COVID-19 was higher in the 9 (0.5%) patients with epilepsy than in the 511 (0.1%) patients without epilepsy. The case fatality rate was higher in suspected COVID-19 patients with epilepsy than in controls, but when only confirmed (positive PCR) COVID-19 patients were included there was no significant difference in fatality rate between epilepsy and nonepilepsy patients. Of the 21 epilepsy patients, more than half were disabled and one-third were institutionalized.

This study has limitations that affect its generalizability. The first is that the prevalence of epilepsy varies based on study methodology and geographic location. Although the methodology of using a Spanish prevalence of 0.579% of epilepsy is logical, that number is lower than in other studies. For example, between 2013 and 2015 in the US National Health Interview Survey of the Centers for Disease Control, 1.1% of US adults reported having active epilepsy (a health care provider told them they had epilepsy or seizure disorder, they were taking anti-seizure medications for a seizure, or they had at least one seizure in the prior year).[7] By contrast, an international meta-analysis calculated a prevalence of 0.64%[8] and a recent Latin America systematic review and meta-analysis found an active prevalence of 0.9%.[9] Although rates may indeed differ among different populations, a major problem is the wide variation in the completeness of case ascertainment and the definitions of epilepsy used in studies on the epidemiology of epilepsy. If the Spanish prevalence is actually higher, then the cumulative incidence of epilepsy patients with COVID-19 is probably not statistically different from the control population.

A second limitation is that 1 of 3 of the epilepsy patients with COVID-19 in the University of Malaga emergency department in March to April 2020 came from institutions. That percentage is much higher than the living situation of most people with epilepsy. This time frame was at the early point in the pandemic when long-term care (LTC) facilities were being preferentially affected. At the time of this writing, the situation worldwide is very different with most COVID-19 cases and deaths coming from the general community. As a result, a similar study should be repeated to see whether overrepresentation of patients living in LTC facilities was a confounder.

A third limitation, which the authors acknowledge, is that PCR testing for SARS-CoV-2 was not widely available at the early stage of the pandemic during which the study was conducted. In their study, deaths from COVID-19 were not different between the 2 groups who had PCR-confirmed disease.[6] Testing is now widely available. Therefore, a new study including only test-proven COVID-19 patients should be conducted.

In conclusion, COVID-19 is not proven to be more common in epilepsy patients, and mortality from COVID-19 is not proven to be higher in epilepsy patients, than in controls based upon this study. Further research is warranted using persons with epilepsy residing in more representative living situations and using PCR confirmation in all patients.

By David G. Vossler

ORCID iD

David G. Vossler https://orcid.org/0000-0003-4823-0537

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