Epilepsy & Behavior 108 (2020) 107122

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Letter to the Editor

# Epilepsy and COVID-19: Associations and important considerations

*To the Editor*

## 1. Introduction

Coronavirus disease 2019 (COVID-19) is a novel infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the outbreak, which initially occurred in Wuhan, China in late 2019, is now rapidly spreading globally [1]. The world is expected to implement early precautionary measures to control the spread of COVID-19 through restriction of activities.

Epilepsy, a disease characterized by a spontaneous recurrence of unprovoked seizures, is one of the most common chronic neurological conditions. Its prevalence rate is reported to be 0.7–1.0% with high incidences in elderly people and children [2]; additionally, some patients have comorbidities.

Associations between epilepsy and COVID-19 have not been reported. Here, we discuss the important considerations for patients with epilepsy by reviewing known facts of COVID-19 and suggestions from medical societies associated with epilepsy, as well as inferring from past experiences of infectious diseases.

### *1.1. Could people with epilepsy be a higher risk for COVID-19 than other people?*

The Center for Disease Control and Prevention (CDC) suggests that neurological comorbidities, including epilepsy, may be a risk factor for COVID-19, despite the lack of evidence. Presently, a medical history of epilepsy has not been reported to be a risk factor for developing COVID-19. Moreover, past experiences with infectious diseases do not suggest any associations. Considering the experience with previous infectious diseases, some societies suggest that epilepsy itself seems unlikely to represent a risk factor for COVID-19 (Table 1). However, certain preexisting conditions (such as smoking, obesity, diabetes, heart disease, lung disease, and cancer) are recognized as risk factors [3,4]. Therefore, patients with epilepsy with these comorbidities may adopt a more cautionary approach regarding COVID-19. Conversely, children infected with COVID-19, including those just with well-controlled epilepsy and no other health conditions, are generally asymptomatic or present with mild symptoms [5].

Coronavirus disease 2019 prevention strategies recommended by the CDC are applicable to all individuals, including those with epilepsy.

### *1.2. The effect of COVID-2019 on patients with epilepsy*

Baig et al. suggested that the central nervous system could be a potential target of SARS-CoV-2 as the angiotensin-converting enzyme two receptors have been detected on the surface of glial cells and neurons [6,7].

However, the effects of COVID-19 on patients with epilepsy and the prevalence of new-onset epilepsy cases remain unclear. Reported symptoms of COVID-19 are primarily associated with respiratory or gastrointestinal issues and have not been commonly related to seizures [8]. According to previous data, the rate of neurological comorbidity has not been assumed to be greater for COVID-19 than other respiratory viral infectious diseases. Conversely, patients with epilepsy infected with COVID-19 or any other infectious diseases may have fever, which may possibly trigger seizures.

Additionally, the association between antiepileptic drugs (AEDs) and medications for COVID-19 requires consideration. Currently, no specific medications have been approved for COVID-19; however, several preexisting medications have been tested for the treatment of COVID-19 with a few of them showing potential. Epileptologists may have good knowledge about the interaction between these medications and AEDs. The Italian League Against Epilepsy provides a table of interactions of these drugs (https://www.lice.it/pdf/Antiepileptic_drugs_interactions_in_COVID-19.pdf). Certain combinations are not recommended or require greater attention to prevent the inductions of critical comorbidities. Levetiracetam is of interest, as it would not cause interactions with any drug. Drug interactions should be taken into consideration when introducing or adding AEDs. Moreover, some medications for supportive treatment such as antihistamine would reduce seizure threshold.

Certain epilepsy medications may affect the immune system, including everolimus and steroids that are used for tuberous sclerosis complex and autoimmune epilepsy, respectively. However, according to some studies, everolimus may prevent viral infections [9]. Meanwhile, the usage of corticosteroids is correlated with the risk of infectious diseases [10]. Hence, medications need to be chosen on an individual basis in clinical settings. Furthermore, some societies do not recommend changing the AEDs of patients with well-controlled seizures, as seizure exacerbations or status epilepticus may increase the risk of COVID-19 infections. It is also important in clinical settings to inform patients that they should not discontinue AEDs without the advice of a physician, even if it would affect the immune systems.

Some societies suggest that COVID-19 could increase the risk of sudden unexpected death in epilepsy (SUDEP). There are some reports that indicate that infection or viral infectious disease might increase the risk of SUDEP [11,12]. However, there are still no data on the association between COVID-19 and SUDEP.

https://doi.org/10.1016/j.yebeh.2020.107122

**Table 1**
A summary of the suggestions made by various associations and societies for patients with epilepsy [20–32]. COVID-19: coronavirus disease 2019, AEDs: antiepileptic drugs, SUDEP: sudden unexpected death in epilepsy, CURE: Citizens United for Research in Epilepsy, AES: The American Epilepsy Society.

*1: It depends on other underlying health issues.
*2: Yes, as with other viral infections.
*3: Call your healthcare team for advice.
*4: Ask someone to pick up your AEDs or ask your pharmacy if they can arrange home delivery if you need to self-isolate.

### *1.3. Importance of maintaining seizure control in COVID-19 crisis*

Many societies recommend that patients should avoid running out of AEDs. The state of increased or uncontrollable seizures could cause some problems. One is the effect of seizure on the patient's body condition. Mortality associated with epilepsy is higher in patients with uncontrollable seizures than in those with controllable seizures [13,14]. Frequent seizures would cause malnutrition, and the state of nutrition is associated with the immune system [15]. The second problem is that going to emergency rooms because of increased or uncontrollable seizures could expose the patient to coronavirus. The Epilepsy Foundation does not recommend going to emergency room unless there is an actual emergency. Finally, uncontrollable seizures, especially status epilepticus, would need sedation and ventilators. However, in clinical settings at regions with many patients with COVID-19, clinicians face the shortage of mechanical ventilators [16]. Increase in the number of patients with status epilepticus would aggravate this problem.

Therefore, it is very important to maintain the control of seizures, as well as the prevention of COVID-19. However, visits to doctors and periodic filling of prescriptions account for the greater difficulty encountered by patients with epilepsy in avoiding crowded situations. Previous experience with SARS evidently shows that emerging infectious diseases can potentially prevent patients with epilepsy from keeping up with their routine appointments [17]. This can be mitigated through the introduction of telemedicine and purchase of prescription medications lasting a minimum of a few months. Telemedicine allows consultations with doctors without exposure to crowded conditions, and thus prevents the spread of COVID-19 among patients. Hence, introduction and implementation of telemedicine should be given further consideration.

### *1.4. Suggestions for epilepsy monitoring units and surgery*

Intractable epilepsy may be assessed and diagnosed by video-monitoring encephalograms and hospitalization. Elective surgical treatments for epilepsy, along with other nonurgent surgical procedures, may be postponed to prevent further spread of COVID-19 among medical staff and patients [18]. Hospitals should rather prepare for the increasing number of patients with COVID-19 who will require critical care.

Patients with epilepsy who require urgent interventions, along with their families and medical staff, should adhere to thorough prevention and protection protocols against COVID-19.

Some patients do not have emergency but progressive conditions of epilepsy. As for these cases, the real risk of proceeding and the real risk of delay on intervention should be considered case by case.

### *1.5. Considerations for caregivers or patients who live alone*

Patients with epilepsy may be dependent on caregivers. Patients with epilepsy suspected to be infected with COVID-19 should be isolated; the caregiver should seek treatment, especially through oral care or aspirations, for prevention and protection against COVID-19. Protection against COVID-19 also necessitates the treatment of COVID-19 carriers.

Caregivers infected or suspected to be infected with COVID-19 should stop providing care to their patients and isolate themselves. They may also find replacements for their clients for the time being.

As for patients with epilepsy who live alone, it is suggested to keep regular contact with someone to inform that they are alright while self-isolating, especially patients with uncontrolled seizures.

## 2. Importance of spreading awareness

It is important to provide this information to patients with epilepsy and their families so that they may be prevented from being infected with COVID-19. Additionally, the spread of correct information will reduce unnecessary anxiety and stress. According to Hu M. et al., educating patients with epilepsy would reduce seizure frequency and accidental injuries caused by seizures [19]. Conversely, internet and social media can be a source of informal, uncertain, or misleading information that may cause people to respond erroneously or panic unnecessarily. A system for disseminating reliable resources of information needs to be established. A few medical associations and societies have provided useful information regarding epilepsy and COVID-19 (Table 1) that may be shared. Translations and subsequent dissemination of these resources can also aid patients with epilepsy globally. Moreover, the American Epilepsy Society has also provided information and attention points for clinicians.

## 3. Conclusion

This article reviewed known facts of COVID-19 associated with epilepsy and the suggestions from medical societies. The effect of COVID-19 on individuals with epilepsy remains unclear. Clinicians need to share case information, continue investigations, and provide known facts to patients with epilepsy and their families.

## Financial disclosures

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Declaration of competing interest

None.

## Acknowledgments

None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2020.107122.

## References

[1] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. Epub 2020 Mar 27.
[2] Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon CS, Dykeman J, et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. Neurology 2017;88:296–303.
[3] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. Jama 2020;323(13):1239–42.
[4] Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. BMJ 2020;368:m1198.
[5] Lu Q, Shi Y. Coronavirus disease (COVID-19) and neonate: what neonatologist need to know. J Med Virol. Epub 2020 Mar 1.

[6] Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Nerosci 2020 Apr 1;11(7):995–8.
[7] Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol. Epub 2020 Feb 27.
[8] Sun T, Guan J. Novel coronavirus and central nervous system. Eur J Neurol. Epub 2020 Mar 26.
[9] Tan L, Sato N, Shiraki A, Yanagita M, Yoshida Y, Takemura Y, et al. Everolimus delayed and suppressed cytomegalovirus DNA synthesis, spread of the infection, and alleviated cytomegalovirus infection. Antiviral Res 2019;162:30–8.
[10] Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. Arthritis Rheum 2006; 54:628–34.
[11] Andersen ML, Tufik S, Colombo AL, Cavalheiro EA, Cysneiros RM, Scorza FA. Sudden unexpected death in children with epilepsy: the many faces of fungal pathogenicity. Med Hypotheses 2012;79:127–8.
[12] Wang J, Huff K, McMasters R, Cornford ME. Sudden unexpected death associated with HHV-6 in an adolescent with tuberous sclerosis. Pediatr Neurol 1999;21: 488–91.
[13] Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Clinical risk factors in SUDEP: a nationwide population-based case–control study. Neurology 2020;94: e419–29.
[14] Krijgh EJC, Catsman-Berrevoets CE, Neuteboom RF. Early seizure freedom is a prognostic factor for survival in patients with West syndrome. Neuropediatrics 2018;49: 279–82.
[15] Crepin S, Godet B, Chassain B, Preux PM, Desport JC. Malnutrition and epilepsy: a two-way relationship. Clin Nutr 2009;28:219–25.
[16] Truog RD, Mitchell C, Daley GQ. The toughest triage — allocating ventilators in a pandemic. N Engl J Med. Epub 2020 Mar 23.
[17] Lai SL, Hsu MT, Chen SS. The impact of SARS on epilepsy: the experience of drug withdrawal in epileptic patients. Seizure 2005;14:557–61.
[18] Iacobucci G. Covid-19: all non-urgent elective surgery is suspended for at least three months in England. BMJ 2020;368:m1106.
[19] Hu M, Zhang C, Xiao X, Guo J, Sun H. Effect of intensive self-management education on seizure frequency and quality of life in epilepsy patients with prodromes or precipitating factors. Seizure 2020;78:38–42.
[20] The Epilepsy Foundation. Concerns about COVID-19 (coronavirus) and epilepsy. https://www.epilepsy.com/article/2020/3/concerns-about-covid-19-coronavirus-and-epilepsy/;, Accessed date: 13 April 2020.
[21] The Epilepsy Foundation New England. Coronavirus information for people affected by epilepsy in New England. https://epilepsynewengland.org/news/coronavirus-information-for-people-affected-by-epilepsy-in-new-england/;, Accessed date: 13 April 2020.
[22] Epilepsy action. Coronavirus (COVID-19) and epilepsy. https://www.epilepsy.org.uk/info/daily-life/safety/coronavirus-covid-19/;, Accessed date: 13 April 2020.
[23] The Epilepsy society. Epilepsy and the coronavirus (COVID-19) FAQs. https://www.epilepsysociety.org.uk/epilepsy-and-coronavirus-covid-19-faqs#.XnzOrIj0mUl/;, Accessed date: 13 April 2020.
[24] The BC Epilepsy Society. Does epilepsy put me at a higher risk of developing COVID-19? http://bcepilepsy.com/blog/does-epilepsy-put-me-at-a-higher-risk-of-developing-covid19/;, Accessed date: 13 April 2020.
[25] The BC Epilepsy Society. Can COVID-19 affect my seizures? http://bcepilepsy.com/blog/can-covid19-affect-my-seizures/;, Accessed date: 13 April 2020.
[26] CURE (Citizens United for Research in Epilepsy). COVID-19 and epilepsy. https://www.youtube.com/watch?v=9gMj4n6Jndc/;, Accessed date: 13 April 2020.
[27] AES (The American Epilepsy Society). Covid-19 resources for epilepsy clinicians. https://www.aesnet.org/about_aes/position_statements/covid-19/for-clinicians/;, Accessed date: 13 April 2020.
[28] The Young Epilepsy. Information about COVID-19 (coronavirus). https://www.youngepilepsy.org.uk/covid-19-information.html/;, Accessed date: 13 April 2020.
[29] Epilepsy Scotland. Coronavirus (Covid 19) — what you need to know if you have epilepsy. https://www.epilepsyscotland.org.uk/coronavirus-covid-19-what-you-need-to-know-if-you-have-epilepsy/;, Accessed date: 13 April 2020.
[30] First Choice Neurology. Epilepsy and COVID-19 — first choice neurology — Dr. Andrew Lerman. https://www.youtube.com/watch?v=71XdG8bDYA0/;, Accessed date: 13 April 2020.
[31] Dravet Syndrome news. Information about COVID-19 for Dravet syndrome patients. https://dravetsyndromenews.com/information-about-covid-19-for-dravet-syndrome-patients/;, Accessed date: 13 April 2020.
[32] Dravet Syndrome UK. Latest coronavirus guidance for children and adults with Dravet syndrome. https://www.dravet.org.uk/news/coronavirus-advice/;, Accessed date: 13 April 2020.

Naoto Kuroda
*Department of Pediatrics, Children's Hospital of Michigan, Wayne State University, Detroit, MI, USA*
*Department of Pediatrics, Children's Hospital of Michigan, Wayne State University, Detroit Medical Center, 3901 Beaubien St., Detroit, MI 48201, USA.
*E-mail address:* naoto.kuroda@wayne.edu

13 April 2020