Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Epilepsy and COVID-19: Updated evidence and narrative review

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ABSTRACT

The coronavirus disease 2019 (COVID-19) outbreak started in Wuhan, China, in late 2019 and rapidly spread globally. Vaccines have recently been developed and are being administered in some countries, but their widespread use is not yet sufficient; the battle against COVID-19 is protracted and people need to adapt to living under the influence of this disease. Epilepsy is a common chronic neurological condition characterized by spontaneous recurrence of unprovoked seizures. Various effects of COVID-19 on epilepsy have been studied in recent months. As clinicians, we need to keep up with daily updates in the evidence regarding interactions between COVID-19 and epilepsy. This review article summarizes the current evidence. Prospective studies on epilepsy and COVID-19 remain lacking. Most articles have comprised case reports, case series, retrospective studies, and recommendations/opinions that do not include data. However, summarizing these articles can identify the demands for research into COVID-19 and epilepsy by clarifying what is known and what remains unclear from current research.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a novel infectious disease caused by severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2). This disease represents one of the most significant pandemics in human history [1]. Research into COVID-19 from multiple perspectives is underway around the world to address the threats from this disease. Severe acute respiratory syndrome coronavirus 2 is a virus that targets angiotensin-converting enzyme 2 receptors, which are found not only in the lower respiratory tract but also in the cells of multiple organs, including the brain. Investigations into the effects of COVID-19 on the nervous system are thus of interest to many neurologists. Many papers have already been published on the effects of COVID-19 on the nervous system, only several months since the pandemic began.

Epilepsy, a disease characterized by a spontaneous recurrence of unprovoked seizures, is one of the most common chronic neurological conditions. The prevalence of this pathology is reported as 0.7–1.0%, with high incidences among elderly individuals and children [2]. Various factors surrounding epilepsy may be affected by COVID-19 (Fig. 1), and care for patients with epilepsy in the COVID-19 era thus needs to take such factors into account. Consideration of the relationship between epilepsy and COVID-19 is clearly important.

We have already discussed the relationship between epilepsy and COVID-19 [3]. However, in the field of epilepsy, as in other fields, the evidence associated with COVID-19 has continued to be updated daily in recent months (Fig. 2). We therefore review and discuss the latest evidence on epilepsy and COVID-19.

2. Associations between COVID-19 and epilepsy/seizure

2.1. Could individuals with epilepsy be at higher risk of COVID-19 than others?

As we have discussed before [3], the Centers for Disease Control and Prevention (CDC) had suggested that neurological comorbidities, including epilepsy, may be risk factors for COVID-19, despite a lack of evidence. However, this statement was later removed from the CDC website. One cross-sectional study investigated whether patients with active epilepsy may be at risk of

Abbreviations: AAN, American Academy of Neurology; ACNS, American Clinical Neurophysiology Society; AEDs, antiepileptic drugs; AES, American Epilepsy Society; CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; EEG, electroencephalogram; ICU, intensive care unit; ILAE, International League Against Epilepsy; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SE, status epilepticus; TSC, tuberous sclerosis complex; VNS, vagus nerve stimulation.

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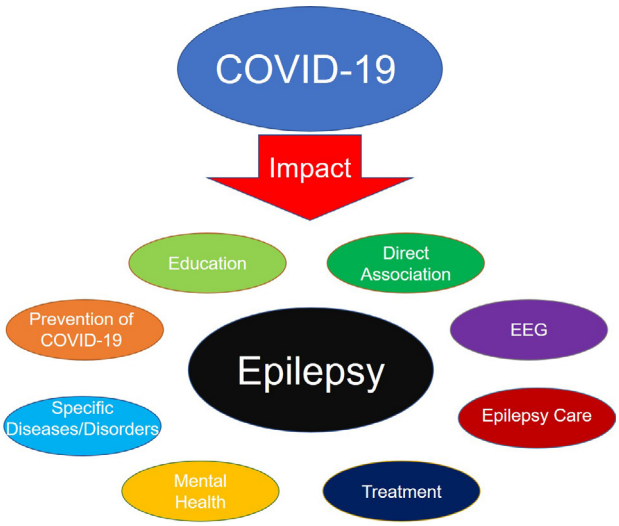

Fig. 1. Epilepsy and associated issues that may be affected by COVID-19. COVID-19, coronavirus disease 2019.

COVID-19 compared to a control group [4]. According to that study, active epilepsy would be an independent risk factor for both the incidence and mortality of COVID-19. In that study, active epilepsy was associated with a 5.1-fold greater odds ratio of mortality risk. However, that interpretation of the results should only be accepted with caution, because the study showed the limitation of including probable and possible cases that remained unconfirmed as COVID-19-positive by polymerase chain reaction testing. The active epilepsy group in that study included 12 possible/probable cases, accounting for fully 57% of the group. Conversely, another study in Spain and Italy reported that among 5700 patients with epilepsy managed at three epilepsy centers, only 14 tested positive for COVID-19 without any obvious impact on epilepsy [5]. Based on the limitations of the first study and the inconclusive results of the second study, it is probably too early to determine that epilepsy is a risk factor for COVID-19. A systematic review article showed that the rate of COVID-19 severity in people with epilepsy is lower than other neurological disorders such as dementia, cerebrovascular disease, and multiple sclerosis [6]. In addition, epilepsy is not a single disease, and has many causes and associations, some of which may debilitate the patient and increase the risk of respiratory or other independent risk factors. Research looking at different groups of epileptics is also needed to determine which patients with epilepsy are truly at higher risk.

2.2. Could COVID-19 cause acute symptomatic seizures?

Acute symptomatic seizures can be caused by poor general condition, mainly fever, arising from infection. This would also apply to COVID-19, and the incidence of this etiology represents an important concern for emergency department physicians and neurologists. Several papers have investigated the incidence of acute symptomatic seizures, but a more comprehensive determination is needed given the multifactorial influence of COVID-19 on disease severity and other background conditions. Various studies have reported the incidence of acute symptomatic seizures due to COVID-19 as less than 1% [5,7–9]. This is lower than the seizure rates previously reported for SARS (2.7%) and Middle East respiratory syndrome (8.6%) [10,11], suggesting that acute symptomatic seizures caused by COVID-19 are not particularly common compared with other viral diseases.

We should also note the lack of reports on seizures among COVID-19 presentations in the general population. In fact, acute symptomatic seizure has not been mentioned in several studies that summarized the symptoms of a large sample of COVID-19 patients [1,12,13].

2.3. Would patients with epilepsy experience worsened seizures during the COVID-19 crisis?

COVID-19 effects exerted not only directly on the human body but also indirectly through the wider influences on society should be considered. Several studies have reported on changes in seizure frequency among patients with epilepsy during the COVID-19 crisis, regardless of whether these patients were infected with COVID-19 [14–18]. According to those studies, the proportion of patients experiencing increased seizures varied from 8–35%, and may reflect factors such as the status of COVID-19 infection in different locations and the proportion of individuals with an at-risk background (e.g., older age) [19]. In fact, the study that reported the lowest rate of seizure exacerbation included less than 2% of

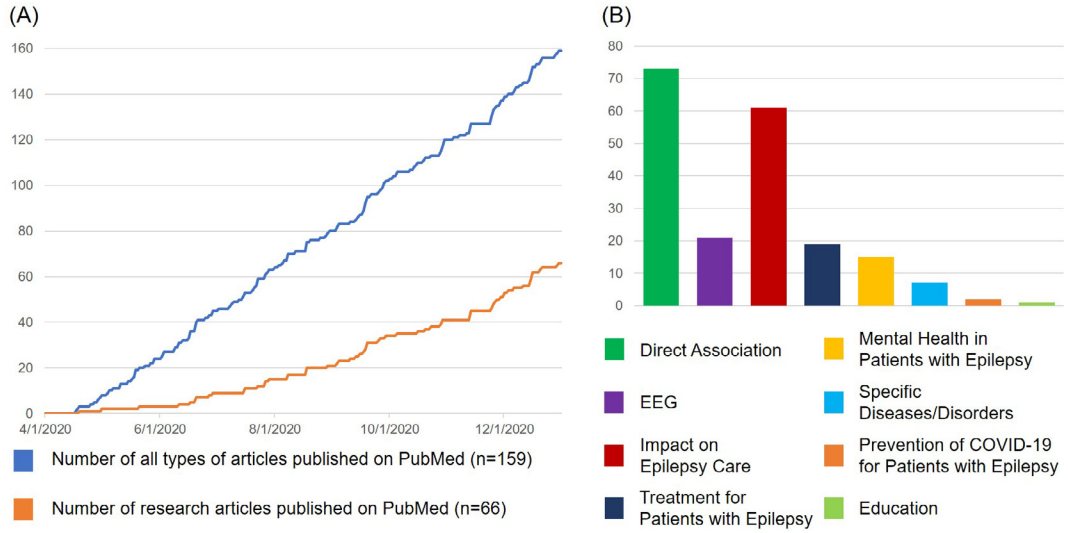

Fig. 2. Published articles about COVID-19 and epilepsy. We found 159 meaningful English articles on PubMed using search terms ((COVID-19) AND (epilepsy)) up to December 31, 2020. (A) Number of meaningful English articles about COVID-19 and epilepsy from Pubmed over time. (B) Number of meaningful English articles from PubMed about COVID-19 and epilepsy, grouped by topic. COVID-19, coronavirus disease 2019.

patients over 60 years old and 31% of patients in their teens [17]. We also should consider differences in dates and countries. The study was conducted up to March 5, so the data can be considered earlier than other studies, although reported from China [17]. Some studies have reported risk factors for seizure exacerbation, and similar factors such as the number of antiepileptic drugs (AEDs), seizure frequency at baseline, sleep-related problems, and mental stress have likewise been reported from separate studies (Table 1) [15–18]. On the other hand, in a study involving three epilepsy centers in Italy and Spain, no significant changes in seizure frequency were reported during the COVID-19 emergency, and, more surprisingly, the number of calls from patients decreased significantly [5]. One explanation was that stay-at-home orders or quarantine due to COVID-19 would allow patients with epilepsy to live a regular life. The lifestyle modifications imposed by the lockdown, improved compliance with treatment, and sleep regularity may have led to better seizure control [5]. On the other hand, increased stress and lack of access to physicians or medication refills, particularly during the early months of service shutdowns, would likely have worsened seizure control during the COVID-19 crisis.

Whether seizures increase in patients with epilepsy during the COVID-19 crisis would depend to a large extent on how their lives and societies are affected by COVID-19, the degree of psychological stress they experience related to its effects, whether they live in an area where COVID-19 is endemic, the quality of epilepsy care in the area during the COVID-19 crisis, and the background of each individual patient.

2.4. Comorbidity of patients with epilepsy and COVID-19

Epilepsy is not a disease, but rather a symptom complex with a very high burden of comorbidities. Patients with epilepsy can therefore show an extremely wide variety of comorbidities and backgrounds. Thinking about the relationship between these and COVID-19 is as important for clinicians as thinking about the relationship between epilepsy and COVID-19. For example, if an individual with epilepsy is elderly, the risk of severe COVID-19 illness is higher than that in the general population, requiring more vigilant infection control measures. Furthermore, as discussed previously [3], the risk is even higher if individuals have other comorbidities that may put them at elevated risk of COVID-19. Stroke, a widely known cause of epilepsy in the elderly, greatly reduces activities of daily livings and weakens patient immunity. This could increase the risks of infection with COVID-19 and subsequent severe illness. Pediatric patients with epilepsy who have neurodisability or underlying brain conditions are more likely to develop pneumonia or other respiratory complications [20]. These respiratory conditions could represent risk factors for COVID-19.

In addition, close attention should also be paid to the background of patients. For example, if a patient lives in a nursing home, concern about outbreaks is warranted [21]. Another study showed that even among patients with epilepsy and multiple comorbidities, a high percentage of asymptomatic individuals was observed, suggesting that epilepsy-related factors do not necessarily lead to poor outcomes [22]. Further research into the risks of COVID-19 arising from complications and environment in patients with epilepsy is still needed.

2.5. Epilepsy as a neurological complication of COVID-19

Unlike acute symptomatic seizures, epilepsy is a chronic condition involving recurrent seizures that occur a certain time after the cause of the seizure. The incidence of epilepsy caused by COVID-19 is not yet known [23], and any such investigation will require a sufficient follow-up period at least in the order of multiple months.

Table 1
Impact of COVID-19 on patients with epilepsy and factors potentially associated with vulnerability. AED, antiepileptic drug; COVID-19, coronavirus disease 2019.

Study, country, period	Clinical impact	Associated factors
Alkhotani et al. [15] Saudi Arabia, April	Seizure worsening46/156 (29.5%)	Number of AEDs Seizure frequency at baseline Noncompliance with medication regimen Change in sleep pattern Increase in self-reported stress
Assenza et al. [16] Italy, 4/11–4/16	Seizure worsening67/456 (18%)	Number of AEDs Severity of sleep disorder
Huang et al. [17] China, 2/23–3/5	Seizure worsening31/362 (8.6%)	History of exposure to COVID-19 Uncontrolled seizure after AED therapy Seizure frequency at baseline Change in AED regimen during outbreak Stress about adverse impacts of outbreak
Fonseca et al. [18] Spain, 3/16–4/17	Seizure worsening 25/255 (9.8%)	Tumor-related epilepsy Drug-resistant epilepsy Insomnia Fear of epilepsy Income reduction
Alkhotani et al. [15] Saudi Arabia, April	Increased stress 85/156 (54.4%)	Occupational status Less than 5 years of epilepsy Psychiatric disease Use of psychiatric medications
Hao et al. [58] China, 2/1–2/29	Increased stress33/252 (13.1%)	Time spent paying attention to COVID-19 Diagnosis of drug-resistant epilepsy
von Wrede et al. [36] Germany, 3/23–5/8	Satisfaction with telemedicine197/239 (82%)	Younger age Non-native speaker Shorter duration as patient in the department Longer duration of epilepsy (negative predictor)
	Wish for future onsite appointments178/239 (74%)	Longer duration of epilepsy Taking anti-seizure drugs Longer duration as patient in the department

We therefore do not currently have clear answers to a variety of clinical questions, such as who is likely to develop epilepsy due to COVID-19, what kinds of seizures are likely to result, how difficult seizure control will be, or how such seizures will differ from epilepsy caused by other viral infections.

3. Electroencephalograms (EEGs) during the COVID-19 crisis

3.1. Guidance to obtaining EEGs during the COVID-19 crisis

In response to the rapid outbreak of COVID-19, the Latin America chapter of the International Federation of Clinical Neurophysiology provided guidance on performing clinical neurophysiology studies during the COVID-19 crisis [24]. That guidance recommends that patients be assessed for COVID-19 risk by asking them questions about their clinical presentation and epidemiology prior to testing. Depending on the patient's risk, neurophysiology service personnel should take the necessary precautions. In addition, the Italian Society of Neurophysiology, the Italian League Against Epilepsy and the Italian Association of Neurophysiology together proposed guidance on EEG testing [25]. Common items in both guidances included the maintenance of personal protective equipment for healthcare providers, adequate hygiene of equipment for performing EEG, and suitable disinfection of the laboratory space.

In other words, these association focused on two points: (1) elective EEGs were put on hold to free up hospital beds with cases on the rise and to lower the risks of viral infection and spread, with plans to reopen when safe and appropriate; and (2) workflows were adapted to protect EEG technologists, other healthcare workers, and future patients to be recorded, and included types of EEGs to be preferentially performed, removal of hyperventilation as a provocative procedure during EEG recording, provision of proper personal protective equipment, and new protocols for disinfecting labs and recording equipment.

The International League Against Epilepsy (ILAE) commission for surgical therapy developed recommendations for video-EEG (https://www.ilae.org/files/dmfile/Video-EEG-Telemetry-for-Epilepsy-Surgery-2020-08.pdf). The details of this statement are discussed in a later section in ***Epilepsy surgery***. A joint statement by the National Association of Epilepsy Centers, American Clinical Neurophysiology Society (ACNS), American Epilepsy Society (AES), American Society of Electrodiagnostic Technologists, and American Academy of Neurology (AAN) is also available on the ACNS website (www.ACNS.org) for additional information (https://www.acns.org/UserFiles/file/FinalConsiderationsforEMUReopeningJune2020.pdf). This statement provides advice to reopen the Epilepsy Monitoring Unit and continue management.

While important general issues related to conducting EEGs are certainly present during the COVID-19 pandemic, all final decisions on clinical care are also strongly dependent on local governmental rules and regulations, as well as hospital and outpatient clinic policies. Final decisions on conducting EEG during the COVID-19 crisis should be carefully tailored to the specific needs of the local clinical practice situation.

3.2. EEG findings in patients with COVID-19

Several reports have described EEG results in patients affected by COVID-19 [26–30]. In most case series, EEG testing is performed following a seizure or altered consciousness, on suspicion of acute symptomatic seizures or encephalopathy [26–29]. Many of those reports have found no COVID-19-specific findings that would lead to suspicion of COVID-19 infection based on EEG testing [26–28]. According to a study from New York that summarized the EEG findings of 111 patients with COVID-19, past medical history of epilepsy or acute symptomatic seizures prior to EEG was independently associated with epileptiform EEG findings [26]. Another study showed EEG data from 10 consecutive patients affected by COVID-19, divided into groups with good and poor prognosis, and performed quantitative EEG analysis [29]. They showed that brain reactivity was reduced or lost more often in the poor prognosis group than in the good prognosis group.

A large multicenter study is needed to investigate the characteristics of EEG findings in COVID-19 patients.

4. Impact of COVID-19 on epilepsy care

4.1. Restriction of clinical care due to COVID-19

The social impact of COVID-19 is seen not only among individuals with epilepsy but also on epilepsy care facilities. The access of patients to healthcare facilities has been greatly restricted because of the potential for patient-to-patient or healthcare provider-to-patient transmission of SARS-CoV-2. In addition, in hospitals with COVID-19 inpatients or in areas with widespread COVID-19 infection, standby admissions have been severely limited due to fears of patient-to-patient transmission. In fact, in a survey of 212 pediatric neurologists in 49 countries, more than 90% of physicians responding stated that in-person outpatient visits had decreased and use of telemedicine had increased [31]. The same study also found an approximately 90% decrease in EEG. As for the number of EEG tests, a survey of more than 200 Italian centers found a 75% reduction in the number of EEGs during the crisis compared to the pre-COVID-19 baseline, particularly in specific EEGs such as long-term monitoring/ambulatory EEG/polysomnography/video-EEG [32]. The study mentioned earlier that reported on the current status of three epilepsy centers in Italy and Spain found that less than 10% of activities were related to epilepsy care, that all scheduled surgeries (including vagus nerve stimulation (VNS) implantation) were postponed, and that all epilepsy-related hospitalizations and EEGs were emergency cases only [5]. Other outpatient services for new patients were postponed, and AED tapering plans and changes to VNS settings were also postponed.

On the other hand, Italian data on neurological diseases, not only in patients with epilepsy, showed that 641 patients (30%) suspended hospital treatments, physiotherapy or other support interventions, 76 patients (4%) complained about drug unavailability, and 408 individuals (19%) reported subjective worsening of neurological symptoms during the lockdown [33].

Clinical care was certainly limited by COVID-19. However, most of these data were obtained from March to April 2020, a time at which the rapid spread of COVID-19 around the world was forcing clinicians to respond to rapid changes. At this point in time, discussing how to manage clinical practice in the future based on these past data is necessary, depending on the situation. Systems need to be developed to ensure that the restrictions placed on healthcare institutions by COVID-19 do not lead to deteriorations in patient conditions. We thus have to consider potential negative impacts of restriction. For example, delaying certain types of EEGs (specifically, elective EEGs) delays proper diagnosis and treatment for individuals with epilepsy-mimicking conditions and those who are medically refractory and in need of epilepsy surgery, contributing to morbidity and possible mortality such as sudden unexpected death from epilepsy.

4.2. Utility and strengths/weaknesses of telemedicine for patients with epilepsy

As mentioned above, one of the most significant changes healthcare organizations have been forced to make is the switch

from outpatient care to telemedicine. Several studies investigating the usefulness of telemedicine during the COVID-19 crisis have been reported [34–36].

These studies found that nearly 90% of telemedicine visits were by telephone. These data may vary depending on the region from which they are obtained. A Spanish survey found that AED changes were less frequent with telemedicine than with in-person outpatient visits [34]. Another survey from India reported that for teleconsultations in which caregivers were consulted, 74% of reports were seizure-related, 60% of patients in the teleconsultation had experienced an increase in AED dose, and 17% had experienced initiation of a new AED [35]. In both studies, patients, caregivers, and healthcare providers all reported high levels of satisfaction with telemedicine. On the other hand, 40% in the survey conducted in Spain and only 3.2% in the study from India experienced some technical problems [34,35]. These results show that a large number of people experienced communication inconveniences due to technical problems, and in fact about 3% of people were unable to access medical care due to technical problems. This represents a major weakness of telemedicine, and such wide variations between studies can be imagined to be due in no small part to differences in the development of regional telemedicine infrastructure, as well as to the familiarity of medical practitioners and patients with the use of telemedicine. Another recent study suggested that male patients with epilepsy are less likely to make use of telemedicine services. This identifies a vulnerable group and may help to address the needs of these patients. Furthermore, patients experienced supply problems despite being in an industrialized country [37].

According to an article summarizing the pros and cons of telemedicine during the COVID-19 crisis, advantages include the obvious benefits of avoiding exposure to SARS-CoV-2, in addition to the traditionally stated benefits of reducing financial and time burdens on patients and benefits to patients who have difficulty accessing healthcare facilities [38]. On the other hand, telemedicine also arguably has weaknesses in that the ability to perform physical examinations are greatly restricted, clinical tests cannot be performed, and the method is inconvenient for patients with difficulties participating in telemedicine due to hearing or visual impairments. Particularly in terms of physical examinations and observation of adverse effects from AEDs, video telemedicine may be able to address these weaknesses to some degree, but as mentioned above, this may be even more limited when almost all outpatients conduct interactions by telephone.

Considering these strengths and weaknesses of telemedicine, it is important to distinguish between the use of telemedicine and physical visits. In other words, the timing of the switch from telemedicine to in-person outpatient services is important. In this regard, an opinion paper has been released on policy-making in telemedicine for patients with epilepsy using a decision-making tree [38].

Clinicians should make every effort to ensure that patients are not adversely affected by telemedicine, using methods appropriate to the characteristics of the community, hospital, and COVID-19 infection situation.

5. Treatment for patients with epilepsy during the COVID-19 crisis

5.1. AED therapy

Patients with epilepsy, as with the general population, may be treated for COVID-19, and clinicians need to be aware of the potential for interactions between AEDs and COVID-19 therapies. Caution should be exercised, as interactions can either diminish or enhance the effectiveness of drugs, or cause side effects [39]. Some combinations of AEDs and COVID-19 therapies (e.g. the combination of eslicarbazepine/lacosamide and atazanavir/lopinavir/ritonavir) can cause potentially fatal arrhythmias, and the potential for such interactions thus requires special attention according to the Italian League Against Epilepsy (https://www.lice.it/pdf/Antiepileptic_drugs_interactions_in_COVID-19.pdf). Others, such as carbamazepine, phenytoin, and phenobarbital, should be used with caution when in combination with remdesivir, which is often used to treat COVID-19. Notably, levetiracetam has been shown to be largely unaffected by COVID-19 drugs. Consideration should be given to switching to AEDs with less potential for interactions in patients who may need treatment for COVID-19. On the other hand, changing the AED regimen has been reported as a factor associated with increased seizures [17].

Clinicians should therefore fully consider the risks and benefits of changing AEDs to less interactive agents in their treatment decisions. Risk-to-benefit considerations must thus be made to determine whether the potential risks of causing seizures when switching AEDs are outweighed by the potential benefits of reduced drug interactions between AEDs and COVID-19 treatments.

5.2. Diet therapy

Some patients with epilepsy are on a ketogenic diet or other dietary regimens for the purpose of controlling epileptic seizures. Such patients require regular nutritional guidance, which may be difficult to maintain because of the restrictions in place during the COVID-19 crisis. Securing the ingredients for a ketogenic diet may also be more difficult. Thus, patients may experience substantial obstacles to maintaining specific diets under the COVID-19 crisis. However, one letter reported that telemedicine using video chats for five patients enabled all five to continue their diets [40]. The possibilities of telemedicine in terms of providing nutritional guidance are also promising.

5.3. Epilepsy surgery

Surgical treatment may be considered for patients with drug-resistant epilepsy. During the COVID-19 crisis in March–April of 2020, some authorities recommended that elective surgeries be postponed as much as possible [41]. The urgency and prevalence of COVID-19 in each specific region should be considered to determine the overall priority of surgical cases [42]. Epilepsy surgery is most often an elective procedure, but some cases, such as device-related problems involving VNS/responsive neurostimulators/deep-brain stimulation or interventions for refractory epilepsy, should not be postponed [43]. According to the ILAE Commission for Surgical Therapy (https://www.ilae.org/files/dmfile/Video-EEG-Telemetry-for-Epilepsy-Surgery-2020–08.pdf), frequent seizures with injuries, tonic-clonic seizures with high risk of sudden unexpected death in epilepsy and injury, and recurrent episodes of status epilepticus (SE) should be considered as urgent cases for epilepsy surgery rather than elective. They also mentioned that the necessity of video-EEG for preoperative assessment purposes should be carefully considered during the COVID-19 crisis.

On the other hand, as even patients with COVID-19 may require surgery, the risks of surgery in COVID-19 patients should also be considered. A study on surgeries as a whole found that SARS-CoV-2-positive patients are more likely to experience postoperative respiratory complications and are at a greater risk of postoperative mortality within 30 days of surgery, especially for male patients and patients over 70 years old [44]. Emergency surgery was also shown to carry a higher risk of mortality for scheduled surgery and major surgery has a higher mortality rate than

minor surgery. A comprehensive decision needs to be made based on such evidence. Keeping this accumulated information up to date is also important. In particular, evidence is lacking regarding neurosurgery or epilepsy surgery, and more research is needed.

5.4. Immunotherapy/steroids

Some individuals with epilepsy use immunosuppressive drugs and steroids for the purpose of treating the primary disease. Consideration should also be given to whether the use of these immunosuppressants increases the risk of COVID-19 infection or severe disease. No such evidence has yet been reported for patients with epilepsy. However, one important tool is the ability to infer likely results using evidence accumulated from patients receiving immunosuppressive drugs for other diseases.

Several studies have investigated whether patients using immunosuppressive drugs may be at risk of severe COVID-19. In most such studies, immunosuppressive drugs did not present an obvious risk [45–47].

With regard to the risk of COVID-19 in patients with chronic steroid use, one study has been reported in patients with inflammatory bowel disease. According to that study, steroid use was a risk for COVID-19, along with age and the presence of comorbidities [48]. However, more research is needed, as studies on the risks of immunosuppressive drugs and steroids limited to patients with epilepsy have not yet been conducted.

In addition, immunotherapies and steroids have recently been considered as treatment options for severe COVID-19, to limit the immune response to the virus as a major cause of increased disease severity (https://www.covid19treatmentguidelines.nih.gov/).

5.5. Treatment for patients with SE

The treatment of SE in the COVID-19 situation has been reported in an opinion paper, although clear, data-based evidence remains lacking [49]. That article recommended minimizing anesthesia and intensive care unit (ICU) admissions for SE, with proper exclusion of psychogenic nonepileptic status. On the other hand, some case reports have described patients with COVID-19 who presented with SE [50–52]. From those reports, clinicians should be aware of SE as a symptom of COVID-19. In addition, we should note that no case reports with SE have documented SARS-CoV-2 virus CNS infection. SE can be associated with COVID-19, but a direct causal link with the SARS-CoV-2 virus remains uncertain [53].

A recent study found that numbers of admissions due to SE did not differ significantly from previous years, even if other emergency medical conditions were reduced [54]. The authors also mentioned a trend toward less frequent nonconvulsive SE and the loss of female predominance might indicate the presence of an underdiagnosis of SE.

6. Mental health in patients with epilepsy

The extent to which the social impact of COVID-19 is causing mental stress in people has received a great deal of attention [55,56]. In particular, people with epilepsy are affected by COVID-19 in various aspects of their mental health [57]. Several reports have examined the psychological stress on patients with epilepsy, and such patients are reportedly more susceptible to psychological stress from COVID-19 than the general population [15,16,58]. In the two studies that reported on stress in patients with epilepsy, percentages of patients with increased stress differed markedly (54.4% vs. 13.1%) [15,58]. Reasons for this difference could include differences in the percentage of women (62% vs. 50%), who appear vulnerable to stress in this crisis [59], and the percentage of older individuals, who are at risk of more severe symptoms from COVID-19 [19]. Risk factors include time of exposure to information about COVID-19, diagnosis of drug-resistant epilepsy, diagnosis of epilepsy within 5 years of diagnosis, history of psychiatric disorders, and occupational status (Table 1). As discussed in Chapter 2.3, mental stress can also increase seizure frequency and can lead to depression and other mental health problems, so the mental status of patients with epilepsy needs to be actively assessed.

7. Considerations for specific diseases/disorders

7.1. Infantile spasm

Infantile spasms typically occur in the first year of life, with a frequency of around 1 per 2400–5500 live births. The Child Neurology Society issued a statement about the management of infantile spasms during the COVID-19 crisis [60]. That statement consists of several recommendations categorized as either limited (i.e., intended only for the duration of the COVID-19 pandemic healthcare crisis) or enduring (i.e., intended to outlast the pandemic). Recommendations regarding diagnosis include performing the initial outpatient visit remotely (enduring), having parents or caregivers record typical seizures of the patient on video (enduring), asking about the presence of any skin lesions suggestive of tuberous sclerosis complex (TSC) (enduring), and a preference for outpatient EEG over inpatient EEG (limited). Recommendations for treatment include selecting from among adrenocorticotropic hormone, high-dose prednisolone, and vigabatrin, unless contraindications to all three are present (enduring). For patients with TSC, vigabatrin is preferred (enduring). As for the initial treatment for infantile spasms with etiologies other than TSC, initiation of high-dose oral prednisolone in the outpatient setting is preferred (limited). At least weekly follow-up by telemedicine is suggested. We should note that patients with infantile spasm are some of the most fragile patients with epilepsy and require additional special attention.

7.2. Genetic epilepsy

One study evaluated the impact of the pandemic on caregivers and patients with genetic developmental and epileptic encephalopathies in Spain [61]. According to that study, 39 cases (14.1%) reported increased seizure frequency and 87 (30.3%) reported behavioral deterioration during the lockdown. The same study also identified age and difficulties finding AEDs as risk factors associated with seizure increase, whereas risk factors associated with behavioral deterioration were the type of epilepsy, living in a home without a terrace or yard, and caregiver anxiety. That study showed that patients with genetic epilepsy may be particularly vulnerable to the effects of COVID-19 lockdown, and indirectly to health system barriers. At the same time, it is important to remember that the burden on caregivers is increasing.

7.3. TSC

TSC is one of the most common rare diseases, affecting 1 in 6000 live births and causing multisystem morbidities in the brain, kidneys, heart, eyes, and skin [62]. The only approved treatment is the use of mTOR inhibitors (everolimus and sirolimus), originally identified as immunosuppressants. One study focused on the impact of COVID-19 on patients with TSC [63]. That study included 102 TSC patients, with 26 on mTOR inhibitors (everolimus, 17/26 patients, 2.5–10 mg/day) [63]. One TSC patient had confirmed

SARS-CoV-2 infection. Nine additional patients were probable or possible cases. Neither TSC nor use of mTOR inhibitors, including everolimus, increased the risk of COVID-19 in this study.

With respect to everolimus, another study reported that among 111 liver transplant recipients, nine used everolimus. In that study, everolimus was not a severe risk factor for COVID-19 [64]. In another case series, three of 22 kidney transplant patients were treated using everolimus [65]. Everolimus dosages in those patients were reduced to 3–5 ng/ml, and for patients admitted to the ICU, everolimus was discontinued and steroids were used instead. For both of these reports, cases were so few in number that it remains too early to draw conclusions about the evidence. On the other hand, one report argued that everolimus may help alleviate COVID-19 symptoms, arguing that this agent suppresses the inflammatory cascade of COVID-19 [66].

It is important that treatment for patients with TSCs continue during the COVID-19 crisis without undue concern about COVID-19 risks.

8. Difficulties/risks in prevention of COVID-19 for patients with epilepsy

8.1. Social distance

Social distancing is recommended as one of the key prevention strategies for COVID-19. However, maintaining social distance can sometimes be stressful or difficult. One survey showed that 77/94 respondents (82%) were struggling to maintain social distancing [14]. Reasons for these difficulties included having to report to work an essential job (40/77), having to work in order to make ends meet (26/77), caring for others outside the home (22/77), or having social engagements that the individual was unable or unwilling to miss (14/77). The same report suggested that social distancing may be more difficult for people with epilepsy compared to those without epilepsy, as some individuals with epilepsy are restricted from driving due to epileptic seizures and are thus forced to rely on public transportation.

While it goes without saying that social distancing is important for COVID-19 epidemic prevention, we should be aware that this can sometimes be challenging for individuals with epilepsy.

8.2. Wearing masks

According to the World Health Organization, the use of masks is part of a comprehensive package of prevention and control measures that can limit the spread of certain respiratory viral diseases, including COVID-19. One risk was discussed in which wearing a mask could induce hyperventilation in patients with epilepsy due to breathing difficulties [67]. The authors suggested that patients with epilepsy should not be indiscriminately recommended to wear masks, but also mentioned that the suggestion to avoid wearing face masks under any circumstances is probably unreasonable for patients with epilepsy. They concluded that wearing a face mask is probably advantageous in crowded locations, with intermittent breaks in safe locations away from others.

9. Impact on epilepsy education for healthcare providers

COVID-19 poses significant limitations with regard to education for healthcare professionals involved in epilepsy and research on epilepsy, as well as care for individuals with epilepsy. This is because face-to-face contact between healthcare providers is just as limited as face-to-face contact between healthcare providers and patients. Therefore, how to continue medical education and research during the COVID-19 crisis is a very important issue not only in the field of epilepsy, but also in the entire medical field [68,69]. Recently, the ILAE established an educational system on epilepsy that can be taken on the web [70]. Previous studies have shown the effectiveness of tele-education for healthcare professionals about seizure semiology [71]. In addition to ILAE, AES has intensified its online learning with an increased number of professional webinars among other expanded resources (https://www.aesnet.org/professional_education/ask-the-expert-webinar). Attending a professional meeting virtually may offer greater learning opportunities, as in-person professional meetings often make healthcare providers chose between several interesting learning opportunities. AAN also has a learning platform on its website (https://www.aan.com/education-and-research/online-learning-programs/). These tele-education systems are not limited to seizure semiology alone, but extend from basic knowledge including EEG, pathology, and imaging findings to practical knowledge, and further enhancements are expected in the future [70].

10. Conclusion

We have updated and summarized the current reported evidence on COVID-19 and epilepsy. This paper clarifies our current position and remaining scientific gaps.

It should be noted, however, that only a few months have passed since COVID-19 became widespread, and all the studies described here are unavoidably early and retrospective or cross-sectional in design. Accumulation of quality evidence on epilepsy and COVID-19 requires further research activities.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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