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Review Article

Epileptic Crisis, Epilepsy and Covid-19

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Abstract

The seventh known coronavirus that infects humans is the cause of acute respiratory syndrome 2 (SARS-CoV-2), which was described in December 2019, in the province of Hubei, Wuhan (China), where it was reported several patients with respiratory symptoms and pneumonia who had a new coronavirus (2019-nCoV) as the causative agent, initially called "Wuhan virus". This virus spread rapidly causing high morbidity and mortality, in turn, being declared a pandemic by the World Health Organization on March 11, 2020. The document aims to make a generic summary of the scientific evidence available regarding the affectation of the system by SARS-CoV-2 and specifically, the presence of epileptic seizures, as well as the possible affectation in the patient with epilepsy and the recommendations in this regard. To prepare it, the search engine Google Academic and the descriptors COVID-19, SARS-CoV-2, neurological manifestations/complications and epilepsy were used. The Medline, Scielo, Scopus and Medscape databases were used. Numerous authors report the various neurological manifestations that have occurred, including epileptic seizures. An analytical summary of the scientific evidence available regarding the presence of epileptic seizures in previous epidemics due to other coronaviruses and the current pandemic produced by SARS-CoV-2 is carried out, noting that prospective studies should be carried out to determine if the people who experienced acute symptomatic seizures during COVID-19, they may develop subsequent seizures, or the diagnosis of epilepsy can be defined. Adequate guidance is necessary for patients suffering from epilepsy and to insist that they are not more susceptible to being infected by the virus, nor more likely to have serious manifestations of COVID-19. It is worth mentioning that the emotional tension in the face of the pandemic can create instability in the patient with epilepsy and therefore the appropriate pharmacological management and attention to the mental health of these patients should be taken into consideration. The guidelines of the International League Against Epilepsy are listed, which must be taken into account and among them, the pharmacological interactions of antiepileptic drugs and the drugs used in the various action protocols.

Keywords: *Coronavirus; Neurotropism; Seizures/Epilepsy, Mental Health; COVID-19*

Introduction

The seventh known coronavirus that infects humans is the cause of acute respiratory syndrome 2 (SARS-CoV-2), which was described in December of last year, in the province of Hubei, Wuhan (China), where Several patients with respiratory symptoms and pneumonia were reported to have a new coronavirus (2019-nCoV) as the causative agent, initially called "Wuhan virus" [1].

The disease was named shortly after as coronavirus disease 2019 (COVID-19) [2].

The outbreak of respiratory disease associated with the new coronavirus, caused a rapid increase in the number of cases throughout the region and progressively spread to various neighboring countries such as Thailand, Japan and Korea [2] and then to Europe and America, until it was declared a pandemic by the World Health Organization on March 11, 2020 [2,3].

Coronaviruses are a large family of viruses that have been presented as the causative agent of different clinical manifestations ranging from the common cold to a severe global health problem [4].

SARS-CoV-2 is classified within the genus Betacoronavirus, subfamily Orthocoronavirinae and family Coronaviridae. SARS-CoV and MERS-CoV can cause severe disease, while other members of this family, such as HKU1, NL63, OC43, and 229E are associated with mild symptoms [5].

Coronaviruses have remarkable genetic diversity and a high recombination capacity; this explains the interspecies leap of emerging coronaviruses that have affected humans in recent decades [6].

Respiratory viruses can also penetrate the central nervous system (CNS) (neuroinvasion), affect both neurons and glial cells (property known as neurotropism) and induce various neurological pathologies (neurovirulence) [7].

The study of the neurotropic potential of SARS-CoV-2 through pathological samples and its isolation of the endothelium from the cerebral microcirculation, cerebrospinal fluid and brain tissue can further clarify its role in brain damage and its influence on the cardio-respiratory center in the trunk encephalic [8].

This issue has raised various opinions in the international arena in search of a better definition and to make an alert call to the scientific community and practical doctors to be attentive to any neurological sign related to SARS-CoV-2 infection [9].

This document aims to make a generic summary of the scientific evidence available on the affectation of the nervous system by SARS-CoV-2 and specifically, the presence of epileptic seizures, as well as the possible affectation in the patient with epilepsy and the recommendations about.

To prepare it, the search engine Google Academic and the descriptors COVID-19, SARS-CoV-2, neurological manifestations/complications and epilepsy were used. The Medline, Scielo, Scopus and Medscape databases were used.

Clinical manifestations

It has been described by multiple authors that patients infected with the SARS-CoV-2 virus can present in various ways and present, in turn, neurological symptoms, which coincide or could precede pulmonary symptoms and fever [10].

In the descriptions of convenience samples from three hospitals in Wuhan, up to 36% of COVID-19 patients manifested neurological symptoms, although when only severe cases were analyzed, this proportion rose to 46% [10].

The mean incubation period is five days (mean range: 3 - 7, with a maximum of 14 days). During the viral replication phase, which lasts several days, subjects may have mild symptoms as a consequence of the effect of the virus and of the innate immune response. Lower respiratory tract involvement occurs when the immune system fails to stop the spread and replication of the virus and respiratory symptoms arise as a result of the cytopathic effect on lung cells [11].

Patients generally present with fever, dry cough and fatigue, although they may also complain of pharyngeal and abdominal pain, diarrhea, and conjunctivitis [12].

However, many infected individuals may be asymptomatic or have mild symptoms, such as headache, myalgia, and anosmia. The latter in some cases, as an initial symptom. The infection can produce interstitial pneumonia and, in many cases, irreversible damage to the lung tissue that generates serious sequelae or leads to death.

Global mortality is estimated at 8% and is due to respiratory failure resulting from hypoxia or multi-organ failure [13].

Neurological manifestations

Since the first studies carried out, in line with the neurotropic properties of SARS-CoV2, the neurological affectations of this condition have been presented, which are more frequent in cases of severe infection, worsening the prognosis of patients [14].

From the first reports, epileptic seizures are noted, among the manifestations presented, in addition to ataxia, deterioration of the state of consciousness, and in the first stages hyposmia and hypogeusia [15].

Patients with severe COVID-19 are more likely to have neurological symptoms than those with mild forms. Necropsy studies have shown the presence of hyperemic and edematous brain cell tissue, as well as neuronal degeneration [16].

Some investigators have detected SARSCoV nucleic acid in the cerebrospinal fluid (CSF) of the patients and in the brain tissue studied [17].

An initial study in three hospitals in the epicenter of Wuhan, China, retrospectively evaluated (in the period between January 16, 2020 and February 19, 2020), 214 patients with SARS-CoV-2. 36.4% of the patients presented neurological manifestations (78 patients), where central nervous system involvement (24.8%) predominated, followed by damage to skeletal muscle (10.7%) and peripheral nervous system (8,9 %) [18].

Among the manifestations of the CNS are dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia and seizures. The greatest differences between cases of severe and non-severe infection were observed in impaired consciousness and acute cerebrovascular disease ($P < 0.001$ and $P < 0.05$ respectively) [2].

In turn, patients with viral encephalitis, infectious toxic encephalopathy, acute necrotizing hemorrhagic encephalopathy, and ischemic and hemorrhagic stroke have been described, which, in turn, are part of the structural/infectious etiology of the most recent classification of epilepsies [19].

Epileptic crisis/Epilepsy

When addressing this issue, we must analyze the involvement of patients without a history of epilepsy and the presentation of acute symptomatic epileptic seizures and patients with a previous diagnosis of epilepsy.

The first case of SARS-CoV infection with neurological manifestations was reported in 2003. Among the clinical manifestations, the patient had epileptic seizures, in addition to those corresponding to acute respiratory syndrome [20].

Other patients with SARS infection and epileptic seizures were reported later in the literature (2004). In these, the cerebrospinal fluid was positive for coronavirus (SARS-CoV) [21].

Subsequently, in a study of 70 patients (2014) with Middle Eastern respiratory syndrome (MERS) -CoV infection, six patients had seizures (8.6%) and altered mental status, reported in 18 patients (26%) [22].

In a more recent report (2016), of 183 children admitted with clinical suspicion of acute encephalitis, 22 had coronavirus infection (whose type was not specified) through the detection of anti-CoV IgM. Five of these 22 patients had epileptic seizures [23].

These are investigations of patients presenting epileptic seizures, in the course of infection by other coronaviruses.

Epileptic seizures

Regarding the incidence and risk of acute symptomatic seizures in people with coronavirus disease 2019 (COVID-19), a multicenter retrospective study was conducted in patients with COVID-19 from January 18 to February 18, 2020 at 42 hospitals in Hubei province, the epicenter of the epidemic in China; Sichuan Province; and Chongqing Municipality. Data were collected by 11 neurologists using a standard case report form. A total of 304 people were studied, of whom 108 had a serious condition. None in this investigation had a history of epilepsy, or acute symptomatic seizures, let alone status epilepticus. Two people had seizures during hospitalization, which was interpreted in relation to acute stress reaction and hypocalcemia, and 84 (27%) had brain lesions or metabolic imbalances during the course of the disease, which as it is known, increases the risk of epileptic seizures. There was no evidence to suggest an additional risk of acute symptomatic attacks in people with COVID-19. Neither the virus nor the potential risk factors for seizures appear to be significant risks for the development of acute symptomatic seizures in the course of COVID-19 [24].

The authors' analysis suggests that COVID-19 poses minimal risk for seizures during acute illness, although the proportion of severely ill individuals have risk factors, which may increase the propensity to experience seizures. Therefore, risk factors must be addressed immediately to minimize the risk of developing epileptic seizures [24].

Several studies carried out attempt to define the relationship between COVID-19 and epileptic seizures.

Dugue., *et al*. reported a 6-week-old COVID-19-positive male who developed a cough, fever, and two brief episodes of sustained upward gaze and bilateral leg stiffness, which were clinically consistent with the febrile seizure criterion. SARS-CoV-2 and rhinovirus C RNA sequences were detected by nasopharyngeal and anal swabs, but SARS-CoV-2 RNA was not detected in CSF, serum, or plasma. The electroencephalogram did not require typical paroxysmal graph elements. Brain MRI was normal. Laboratory data showed leukopenia. Possibly, COVID-19 contributed to the febrile systemic response by causing seizures [25].

Moriguchi., *et al*. reported a 24-year-old patient with no history of seizures who developed a headache, fatigue, fever and sore throat. On day 5, he had a normal chest X-ray. On day 9, he presented an altered mental state and a generalized seizure. On examination, she had a stiff neck. Laboratory examination showed leukocytosis (dominant neutrophils, relatively decreased lymphocytes). Chest CT showed ground glass opacities. Lumbar puncture required high pressure (> 320 mm H_20), and CSF studies revealed 12 nucleated cells (no red blood cells). SARS-CoV-2 RT-PCR was negative for nasopharyngeal swab specimens, however positive for CSF. Evolutionarily, she presented multiple seizures that required intubation. Meningitis and viral pneumonia were diagnosed. Brain MRI was compatible with right lateral ventriculitis and encephalitis with hyperintense right mesial temporal changes. He was in treatment for pneumonia and encephalitis at the time of publication. This was the first reported case of meningitis/encephalitis with new-onset seizures in the setting of positive CSF for SARS-CoV-2 and significant lung disease despite negative nasopharyngeal swab test [15].

Karimi., *et al*. report a 30-year-old patient, with a history of good health, who was admitted to an Iranian hospital, and had started 5 days before admission with a dry cough and 3 days before with fever and fatigue. Two days before going to the hospital, she had an epileptic seizure during sleep. He continued with recurrent tonic-clonic seizures of generalized onset (up to 5 times a day) and had the last one when he arrived at the hospital. On examination, clouding and temporal disorientation were found [26].

All complementary studies, including cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) of the skull, were normal. However, the nasal and pharyngeal study were positive for COVID-19. The patient was promptly treated with antiepileptic drugs and the rest of the protocolized treatment for these patients, with a good evolution [26].

Sohal and Mansur describe a 72-year-old patient, with a history of arterial hypertension, coronary artery disease with stents, type 2 diabetes, and kidney disease on hemodialysis, complaining of weakness and lightheadedness, after an episode of hypoglycemia. Evolutionarily, he presented worsening of the respiratory symptoms and altered mental status, requiring intubation and transfer to the intensive care unit. The diagnosis of COVID-19 was confirmed and the imaging study revealed chronic microvascular ischemic changes, but no signs of recent bleeding or infarction. On the third day of admission, the patient presented multiple episodes of tonic-clonic movements of the extremities, requiring treatment with antiepileptic drugs. Despite this, the patient continued with the referred episodes for two days, with a frequency of 3 per day. Unfortunately, the evolution of the patient was fatal. The authors suggest that in patients presenting with seizures and altered mental status, the possibility of COVID-19 is suspected [27].

We agree, as do the authors of these studies, that many viruses can play a role in the development of epileptic seizures and in the cause of these, there may be a relationship with a primary infection of the nervous system, as part of the etiology infectious disease described in the most recent classification of epilepsies [18].

Prospective studies should be done to determine if people who have suffered from COVID-19 have a greater risk of developing subsequent epileptic seizures and even define the diagnosis of epilepsy in later months or years as a consequence of the disease.

Epilepsy

There are not many reports of patients with epilepsy, affected by COVID-19. Vollono., *et al*. reported a 78-year-old woman with a history of herpetic encephalitis and medically well-controlled seizures, who presented with focal EEG-supported status epilepticus with right-sided motor symptoms, which were controlled with medical treatment. Serum levels of anticonvulsant medication were not reported. She was afebrile, her chest X-ray was normal and there were no acute findings on brain MRI. However, her labs revealed lymphopenia and thrombocytopenia. She had a history of second-degree contact with three SARS-CoV-2 positive individuals and developed fever hours after initial seizure presentation. Her RT-PCR of naso- and oropharyngeal swab samples were positive for SARS-CoV-2. CSF determination was not performed. She was treated with resolution of the fever and without further seizures or additional serious medical problems. Her antiepileptic medications included valproic acid, which can cause blood dyscrasias, but her lymphopenia and subsequent fever suggested an increased systemic response, which triggered seizures before fever developed and in the absence of lung involvement. There was no direct evidence of viral infection of the CNS. However, non-compliance with medication was also a possible etiology [28].

It is known that the 2019 coronavirus disease (COVID-19) pandemic can affect all people in the world and cause additional concerns for people with chronic conditions, including epilepsy [29].

Acquires, in the opinion of the authors, significant importance, the possibility that patients with epilepsy, become infected with COVID-19 and may increase their epileptic seizures, as in any acute infection, behaving as a trigger for seizures. It is not the viral infection that can cause epileptic seizures, but sepsis itself and, moreover, the accompanying fever and sleep deprivation, especially in children [30].

Proper guidance to patients and family members with epilepsy is necessary, as they must know that they are not more susceptible, nor do they have more risks than other people of contracting COVID-19, nor do they have a deficit in their immune system. This has been confirmed by recent information from countries with experience in the pandemic (China, Italy and the United States), suggesting that people with epilepsy are not more likely to be infected by the virus, nor are they more likely to have severe manifestations of it. COVID-19 because they have epilepsy.

Alotaibi., *et al*. make some considerations through the Saudi Epilepsy Society and in addition to agreeing with the previous criteria, they state that AEDs by themselves are not immunosuppressive, but in rare cases they may present neutropenia related to the use of AEDs and may, in turn, theoretically have higher risk. Also in rare cases in which such patients have immunomodulatory medications, such as steroids or another immunosuppressant, they may present more severe symptoms of COVID-19 [31].

Mental health and epilepsy

It should not be overlooked that emotional stress in the face of the pandemic can create instability in the patient with epilepsy [32].

A cross-sectional study of cases and controls was conducted from February 1 to 29, 2020 approved by the Ethics Committee of the University of Sichuan, considering by the authors that, during epidemic outbreaks, doctors and caregivers should focus not only on the control of epileptic seizures, but also in the mental health of patients with epilepsy, especially those with drug-resistant epilepsy.

After excluding people with psychosis, they found a significantly higher level of distress among epilepsy patients than controls.

This result supports the fact that the patient with epilepsy is at high risk for mental illness. Although only one of the patients had been diagnosed with COVID-19 at the time of the survey, the results are consistent with previous work suggesting a high prevalence of mental health problems among individuals with epilepsy [33].

In the most severely affected area of Wuhan, China and its surrounding cities, a study was designed to assess the influence of the COVID-19 outbreak on epileptic seizures in patients with epilepsy, when the impact caused by the disease was known. The study was carried out, applying a survey prepared for this purpose, as well as questionnaires related to psychological comorbidities, from February 23 to March 5, 2020. The study showed that a minority of patients with epilepsy experienced an exacerbation of seizures during the COVID-19 outbreak. Stress and inappropriate change in AED regimen were associated with an increase in seizures. In relation to these findings, it is considered that stress could be an independent precipitating factor to trigger seizures in some patients with epilepsy [34].

Taking into consideration that the Coronavirus disease 2019 (COVID-19) is an emerging pandemic and that the number of those affected is increasing and countries report new cases every day, there is a generalized anxiety related to this hitherto unknown disease. Accordingly, an investigation of prevalence and risk factors associated with mental health symptoms in the general population in China during the pandemic was conducted. The study was conducted from February 28, 2020 to March 11 of that year and included 34 regions in China in people 18 years of age or older. The results showed that the prevalence of symptoms of depression, anxiety, insomnia and acute stress were high in the study, especially in confirmed or suspected COVID-19 patients and their family members and friends, people with occupations exposed to risks and residents in Hubei province. Severe intervention measures, including quarantine, delayed return to work, were associated with consequent negative mental health states. This in turn implies the need for systematic work with the population, which includes patients with epilepsy, in whom altered mental health leads to the possible presentation of epileptic seizures, as they and their families face even more pressure as their fears are not limited solely to the pandemic, but also include its disorder and treatment. In addition, it is known that people with epilepsy are at increased risk of psychiatric and behavioral disorders that can arise or worsen during times of stress [35].

It is necessary, however, to comment that at present, there is no solid evidence that the virus itself, by direct action on the central nervous system (CNS), causes psychiatric health problems, in addition to the associated confusion and disorientation. with those with severe acute illness [36].

There are several reasons in the different phases of the pandemic that can aggravate psychiatric symptoms in people with epilepsy. Some of the reasons are measures of physical distancing, quarantine, and social isolation. Unemployment and economic difficulties are an additional burden.

In people with epilepsy, anxiety is caused by fear of having seizures, and not having the right help or treatment is an additional burden [37].

In some cases, patients may present with neurological complications such as hypoxic-ischemic encephalitis, encephalitis, and stroke that lead to more serious neuropsychiatric consequences. Mental disorders that are sequelae of brain disease or damage can arise through direct effects of CNS infection or indirectly through an immune response or medical therapy [38].

For all people with epilepsy, this is a difficult time and it is important to actively work to improve mental well-being and exercise to relieve stress.

Alcohol intake and substance abuse, most common during periods of social isolation, should be avoided. Alcohol and certain substances, including benzodiazepines, can temporarily decrease anxiety, but their long-term consequences for epilepsy and mental illness can be devastating.

Healthy sleep habits with a strict routine are a must. Lack of sleep is a trigger for some epilepsy syndromes. Patients with psychiatric disorders (e.g. mood and anxiety) may find it particularly difficult; the relationship between mental disorders and poor sleep quality is well known. In cases of moderate and severe insomnia, the help of online services with a specialist in sleep hygiene may be necessary.

People with psychiatric disorders who need psychological support should know that online therapy is effective and should not be interrupted [39].

Guidelines of the International League against Epilepsy (ILAE)

We suggest that health professionals review the guidelines of the International League Against Epilepsy (ILAE), through its President, Samuel Wiebe [40], which we consider to be of inestimable value both for patients and for the specialists who attend to them.

It is ratified by this, that, so far, there is no evidence of a direct effect of COVID-19 in seizures and epilepsy. However, as has been expressed, patients may experience worsening of seizures, in relation to systemic disease, drug interactions, decreased access to AEDs, and increased stress. Patients with epilepsy need appropriate guidance and corresponding care [41].

The readjustment of antiepileptic medication in the midst of COVID-19 should be taken into account, as directed, only when the attending physician considers it necessary.

Among other aspects, the President of the ILAE mentions the possible interactions of antiepileptic drugs [40] with the drugs that are used in the action protocols regarding the disease.

Considerations to take into account in relation to drug interactions

It is necessary to consider that hydroxychloroquine and chloroquine interact with antiepileptic drugs (AEDs), such as: phenytoin, phenobarbital, primidone and carbamazepine. These medications lower the concentrations of hydroxychloroquine and chloroquine, which may imply that their effectiveness is decreased. Furthermore, it is known that hydroxychloroquine and chloroquine can be the cause of seizures. Therefore, the best option in patients with epilepsy is not to administer them [42].

The best option is to administer antiretrovirals with caution, if their use is considered in medical action protocols. Surveillance should be mainly on liver and cardiovascular functions. Phenytoin reduces blood levels of antiretrovirals by 30 - 50%, which is why some authors suggest in these cases increasing the dose of antivirals [43].

Carbamazepine increases its plasma concentrations with the associated use of Lopinavir/ritonavir, therefore it can cause secondary manifestations and mainly ataxia.

Interferon interactions do not seem important, except for those reported for any patient, but their use in uncontrolled epileptics is limited.

Azithromycin has a risk of cardiac arrhythmias (prolongation of the QT interval, especially in association with hydroxychloroquine and chloroquine). On the other hand, with the combined use of carbamazepine (one of the most widely used AEDs), macrolides increase the levels of this antiepileptic and poisoning and ataxia can occur. The best option is not to administer it in patients with epilepsy, using Carbamazepine and less associated with hydroxychloroquine or chloroquine, in case of suggestion of its use in the protocols of each moment and phase.

Lopinavir/ritonavir decreases plasma concentrations of Lamotrigine (and possibly Phenytoin and Valproate) probably due to induction of the enzyme system by glucoronization [44].

The therapeutic efficacy of many AEDs (Carbamazepine, Lamotrigine, Phenobarbital, Phenytoin) can be decreased when used in combination with hydroxychloroquine or chloroquine.

The activity of many antiepileptic drugs (Carbamazepine, Lacosamide, Perampanel, Phenobarbital and Phenytoin) could be affected by the co-administration of Tocilizumab, through the induction of liver enzymes.

Ritonavir is a potent CYP3A/CYP2D6 inhibitor and can potentially increase plasma levels of cannabidiol, carbamazepine, cenobamate, clonazepam, ethosuximide, lacosamide, perampanel, and zonisamide [45].

Patients treated with enzyme-inducing AEDs (carbamazepine, cenobamate, eslicarbazepine acetate, oxcarbazepine, phenobarbital/primidone, phenytoin) are a significant risk of drug interaction, which are also metabolized by these enzymes (hydroxychloroquine/chloroquine) [46].

CYP3A inducers (Carbamazepine, oxcarbazepine, eslicarbazepine, cenobamate, phenobarbital, phenytoin, topiramate) can also reduce serum levels of lopinavir.

In the co-administration of sofosbuvir with carbamazepine, phenytoin, phenobarbital or oxcarbazepine, a decrease in the serum level of sofosbuvir is expected.

Interactions increasing plasma levels of other drugs.

Co-administration of hydroxychloroquine with potent inhibitors of CYP2C8 and CYP3A4, such as cannabidiol, may result in increased plasma concentrations of hydroxychloroquine [46].

These suggestions and considerations should be taken into account, by the scientific community, to achieve a better evolution of patients with epilepsy and with acute symptomatic epileptic seizures, in the course of the condition due to SARS-CoV-2, for a comprehensive management of the themselves [47,48].

Conclusion

- The SARS-CoV-2 infection shows involvement of the nervous system in its clinical manifestations, and these include epileptic seizures, which should be an alert for health professionals.
- Prospective studies should be carried out to determine whether people who have suffered from COVID-19 are at increased risk of developing subsequent epileptic seizures and even define the diagnosis of epilepsy later.
- There is no evidence that patients with epilepsy are more susceptible to contracting COVID-19, nor are they more likely to have severe manifestations due to SARS-CoV-2 infection.

- The emotional tension in the face of the pandemic can create instability in the patient with epilepsy and therefore, health professionals must take into account the control of epileptic seizures and the mental health of patients.

- Recommendations regarding the control of patients with epileptic seizures/epilepsy in the midst of the pandemic, which include drug interactions, should be considered for adequate comprehensive management.

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