

Neurocysticercosis, Epilepsy, COVID-19 and a Novel Hypothesis: Cases Series and Systematic Review

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Abstract

Background: There have been many patients with neurological manifestations reported in medical literature following a COVID-19 infection. We conducted a literature review to identify patients with coronavirus disease (COVID-19) who presented with Neurocysticercosis (NCC) and associated seizure disorders/epilepsy. Currently, there is a new variant of the COVID-19 virus strain invading South Africa and no indication when this pandemic will end and what kind of tardive sequelae may occur going forward.

Case: We searched the medical literature looking for all publications regarding NCC, Status Epilepticus (SE), Epileptic Seizures (ES), and Epilepsy (Ep), in patients infected by COVID-19.

Based on the therapeutic response of our series, we propose a novel approach for patients presenting NCC, epilepsy and associated with COVID-19. We have hypothesized on the pathogenesis of ES and SE from the NCC/Cytokine Release Syndrome (CRS), SARS-CoV-2/CRS, including the role played by gut microbiota from the enteric nervous system (gut hormones, gut metabolites, inflammatory factors, neuroactive substances, and microbiota-derived products) to the medulla oblongata/hypothalamus-pituitary-adrenal axis via microbiota gut brain axis in ES, Ep and associated depression, plus the mechanism of hyperferritinemia on the overall process. This article is the first publication approaching this comorbidity as far as we know.

Keywords: COVID-19 • SARS-CoV-2 • Neurocysticercosis • Epilepsy • Seizures • Status epilepticus • Neuro-COVID • Gut microbiota-brain axis • Cytokine release syndrome

Abbreviations: AED: Antiepileptic Drug; AD: Alzheimer's Disease; ANS: Autonomic Nervous System; ASD: Autism Spectrum Disorder; ASM: Anti-seizure Medication; BBB: Blood-brain Barrier; BDNF: Brain-derived Neurotrophic Factor; BT: Baricitinib; CBZ: Carbamazepine; CPEC: Choroid Plexus Epithelial Cells; CNS: Central Nervous System; COVID-19: Coronavirus Disease 19; CRP: C-reactive Protein; CRS: Cytokine Release Syndrome; COVID-19: Coronavirus Disease 2019; CSF: Cerebrospinal Fluid; CT: Computer Tomography; DRE: Drug-resistant Ep; EAE: Experimental Autoimmune Encephalomyelitis; Ep: Epilepsy; ES: Epileptic Seizure; FMT: Faecal Microbiota Transplantations; GBA: Gut-Brain Axis; GI: Gastrointestinal; GM: Gut Microbiota; HCoV-229E: Human Coronavirus 229E; HCoV-OC43: Human Coronavirus OC43; HCoV-NL63: Human Coronavirus NL63; HCoV-HKU1: Human Coronavirus HKU1; HF: Hyperferritinemia; HPA: Hypothalamic-pituitary-adrenal Axis; HRV: Heart Rate Variability; ICU: Intensive Care Unit; IEC: Intestinal Epithelial Cell; IFN- γ : Interferon-gamma; IL-6: Interleukin 6; IMB: Intestinal Mucosa Barrier; IVIG: Intravenous Immunoglobulin; LCS: Lacosamide; LEV: Levetiracetam; LMT: Lamotrigine; MA: Microglial Activation; MCA: Middle Cerebral Artery; MERS-CoV: Mild Encephalitis/Encephalopathy with a Reversible Splenic Lesion and Coronavirus; MDD: Major Depressive Disorder; MO: Medulla Oblongata; MOG: Myelin-oligodendrocyte Glycoprotein; MPTP: 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine; MS: Multiple Sclerosis; NLRs: NOD-like Receptors; NPS: Neuropsychiatric Disorders; OCP: Obsessive-compulsive Disorder; PAM: Perivascular-activated Microglia; PHB: Phenobarbital; PBMCs: Peripheral Blood Mononuclear Cells; PD: Parkinson's Disease; PHE: Phenobarbital; PHY: Phenytoin; PSA: Polysaccharide A; PSD: Posttraumatic Stress Disorder; RA: Rheumatoid Arthritis; SARS: Severe Acute Respiratory Syndrome; SCFAs: Short-chain Fatty Acids; SE: Status Epilepticus; SLE: Systemic Lupus Erythematosus; SSD: Schizophrenia Spectrum Disorders; TCGS: tonic-clonic-Generalized Seizures; TCR: T Cell Receptor; Th: T Helper; TNF- α : Tumour Necrotizing Factor-alpha; Treg: T Regulatory; VA: Valproic Acid; 5-HT: 5-Hydroxytryptophan.

Introduction

At the beginning of December 2019, some authors reported an outbreak of a significant number of persons presenting with viral pneumonia of unknown agents. In the following month (January 7, 2020), Chinese investigators identified the respiratory disease's etiological agent and called it the 2019 novel coronavirus (COVID-19) [1-3]. Since then, every month, a significantly high number of cases presenting COVID-19 and neurological manifestations have appeared in the medical literature. Furthermore, in October 2020, a new variant of SARS-CoV-2 (known as 20H/501.V2, B.1.351 or variant had been found in our province (Eastern Cape), South Africa. This variant has multiple mutations in the spike protein, including K417N, E484K, N501Y. At the moment, to write this manuscript, we do not know when this pandemic will end and what kind of sequelae may occur.

COVID-19 can cause severe neurological conditions such as Ischemic Stroke (IS) and hemorrhagic stroke (HS), cerebral sinus venous thrombosis, Epileptic Seizure (ES), Epilepsy (Ep), Status Epilepticus (SE), and encephalopathies. Some authors published several COVID-19 cases presenting with generalized ES [4-12]. Vollono et al. reported a case presenting a focal SE as a unique clinical feature of COVID-19 [13]. Other authors published some COVID-19 and acute epileptic encephalopathy

[11-15] and different therapy for these conditions [16]. In a systematic review done by Ghannam et al., they found two COVID-19/SE cases; one of them had a past medical history of Ep of aetiology [17]. Gelisse et al. reported that some subjects with severe SARS-CoV-2 infection are at risk of subclinical ES or even Nonconvulsive SE (NCSE) and recommended video-electroencephalogram (VEEG) monitoring for this particular condition [18]. Other authors reported patients presenting COVID-19/TCG ES. Nevertheless, one patient did not get a CSF analysis or MRI scan affecting his diagnostic accuracy [19-21]. Some authors have considered that acute ES may be due to swelling of the cerebral cortex (encephalitis) and the brain's direct damage caused by the virus. However, the SARS-CoV-2 has been detected in some patients' cerebrospinal fluid [17-22]. A retrospective study of case series published by Somani and collaborators reported their EEG findings and clinical features in two COVID-19 cases presenting a new-onset SE without previous Ep or ES. The same authors reported high neurovirulence of SARS-CoV-2 based on autopsy's records. They also confirmed viral antigens in the thalamus, hippocampus, mesencephalic regions, and medulla oblongata, regulating cardiorespiratory functions [23].

Recent reports have shown the benefits of Levetiracetam (LEV) to control SE in COVID-19 cases and verapamil mainly for SE stage III (refractory) with SARS-Cov-2 infection [24,25]. In addition, Mohammad et al.

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[26] published the first patient presenting PRES and SARS-CoV-2 with TCG-SE. Simultaneously, other investigators delivered some recommendations to improve SE's management during this pandemic despite the lack of ventilators and ICU facilities [27]. Neurocysticercosis is a zoonotic disorder of the central nervous system secondary to the cysticercus' larval stage infection (*Cysticercus cellulose*) of the pig tapeworm *Taenia solium* (Ts) common helminth to cause CNS infection in human beings. The occurrence of acquired Ep or the syndrome of raised intracranial pressure in a person living in or visiting a region where Ts is endemic or even in close contact with people who have taeniosis should suggest a diagnosis of NCC. This zoonotic parasitic disease may remain asymptomatic for months or even years, and the diagnosis can be confirmed when performing neuroimaging studies. Symptoms and signs are related to the parasite, showing different biological behaviours from one country to another and the host's inflammatory-immunological response. Nevertheless, most of the NCC-Ep patients taking Phenytoin (PHY), Carbamazepine (CBZ), or Valproic Acid (VA) for a good control of their ES respond very well [28,29].

This parasite is transmitted among humans and between humans and pigs. Taeniosis is acquired only by humans after eating raw or undercooked pork meat contaminated with cysticerci, the parasite's larval form. When ingested, the cysticerci migrate to the human intestine, becoming a mature parasite (Taeniosis). These adult worms shed eggs through human faeces that can infect other humans and pigs through direct ingestion or indirect water and food contamination. In developing countries, pigs are often allowed to roam freely, and they can eat human faeces containing eggs or proglottids of Ts. Ingested eggs result in larvae migrating to different parts of the pig or the developing human cysticercosis. A leading site of migration in humans is the CNS (Figure 1). Then, NCC occurs when the cysts develop in the brain, spinal cord, or optic nerve. ES is the most common clinical manifestation of NCC, affecting 66% to 90% of cases [30].

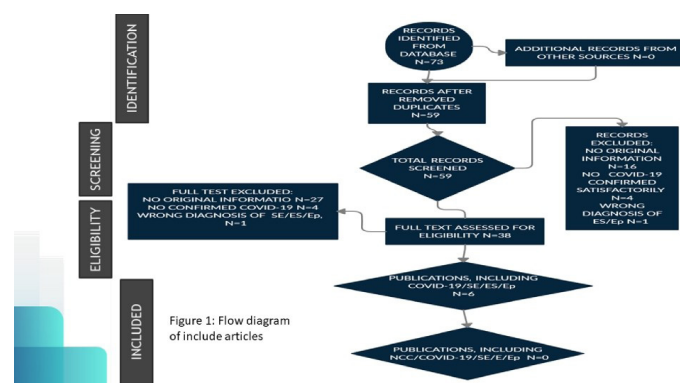


Figure 1. Flow diagram of included publications.

Prevalence of NCC/Ep in our region

The elevated risk of comorbidity between NCC/Ep/ES/SE and COVID-19 infection in this region is secondary to the high prevalence of Ep in our province. Several studies done in different locations along the Mthatha region (South Africa) confirmed a prevalence of Ep between 10 to 15.5%, which is the highest reported in Africa, and this area is the poorest countrywide [31-38]. The estimated prevalence of COVID-19 in this region is not published yet, but this region has one of the highest frequencies of infection countrywide. Today (May, 18th 2021), the total confirmed cases are 1615 485 and total deaths: 55 260, and 478,733 people have been vaccinated [39]. Globally (May 18, 2021), the total confirmed cases are 163 312 429, cumulative death is 3 386 825, and 1 264 164 53 vaccine doses have been administered [40]. Since ancient times, it is common knowledge that NCC causes Ep/ES that SARS-CoV also causes Ep/ES, and both conditions have been reported even before the current pandemic [41]. The first published SARS-CoV case was in 2003, the second one in the following year [42,43]. Later, some epileptic patients associated with other coronavirus types were reported [44]. However, the total number of reported cases is scanty. Nevertheless, there are some reports about SE

and encephalopathy in children as a presentation of COVID-19 infection, and authors reported on the mechanism(s) of production of seizures [45,46]. These authors proposed that ES occurs by direct infection of the virus, post-infectious mechanism, autoimmune response, hematogenous pathway, thrombosis dysregulated cytokine storm, the retrograde neural way, hypoxia, and ACE-2 enzyme mechanism [47,48]. Up to date, nobody has confirmed the comorbidity between NCC and COVID-19; when the current pandemic will stop, or when another epidemic will or may re-emerge. On the other hand, the best treatment for patients presenting NCC/Ep/ES and infected by SARS-CoV-2 remains unknown because no clinical trials have been performed, and there are no published results. This ongoing COVID-19 pandemic carries new challenges regarding the management of NCC and COVID-19 and its complications. NCC's classical treatment now must be performed under novel COVID-19 conditions and regulations, including unique healthcare places, special precautions, restrictions, novel management and strategies, and a new combination of medications, among others. We have research questions: 1. what is the reported frequency of ES/Ep/SE secondary to NCC in a patient infected by COVID-19? Based on that question, an advanced search was conducted in the medical literature.

Literature Review

Literature search strategy

During the initial search (from December 1, 2020, and April 30th, 2021), we included all publications (case reports, case series, and observational cohort studies) reporting NCC/COVID-19/SE/ES/Ep. Later we progressively excluded all duplicate studies and the publications that did not meet the inclusion criteria, and we included only NCC with COVID-19, those that reported Ep, ES, SE related to COVID-19 and NCC. In addition, manuscripts written in Spanish and Portuguese were included, but those in other languages without an English translation were removed.

Study and cohort selection

We searched the following databases: Medline EMBASE, Scopus online databases, Google Scholar, Science Direct, Scielo, LILACS, BIREME, Web of Sciences, and Cochrane library to identify articles evaluating COVID-19 and SE with and without NCC. The Mesh Terms/keywords used for the search included: Neurocysticercosis or epilepsy or brain or status epilepticus or fits or Neuro-COVID or cortical lesions or acute epileptic seizures or seizure or COVID-19 or unconsciousness or refractory epileptic seizure, or intraparenchymal NCC, or Racemose NCC or Subarachnoid NCC or microbiota or gut-brain axis or Zonulin where is the PubMed wildcard for every possible word's used. We did not include other neurological manifestations beyond the current work scope.

Case series

Case 1: A 32-years-old male patient presenting recurrent Tonic-Clonic Epileptic Seizure (TCGS) well controlled with 600 mg of valproic acid twice a day. ELISA NCC was positive. Two months ago CT scan of the brain confirmed an isolated cystic lesion, and he received praziquantel (PZQ) 50 mg/kg/day for two weeks together with 40 mg of Prednisone (PRE) orally daily [49-54]. Two days before admission, the patient complained of generalized vascular headache, recurrent TCGS again, plus mild/moderate fever, general malaise, cough, intermittent abdominal pain, nausea, vomiting, generalized joint pain, remarkable anorexia, scanty urine, and mild depression. PCR confirmed SARS-Cov-2 infection. CT scan of the brain confirmed isolated cysticercus lesion with scolex and ring-enhancing lesion in colloid stage plus peripheral vasogenic oedema (Table 1).

Table 1. Components of cells and its cell count for case one.

Cells	Cell count	
White cell	9.2 × 10 ⁹ /L	3.9-12.6 × 10 ⁹ /L
Hb	13.5 g/dL	12-15 g/dl
Platelets	291 × 10 ⁹ /L	186-454/L

Sodium	141 mmol/L	136 – 145 mmol/L
Potassium	4.2 mmol/L	3.5-5.1 mmol/L
Chloride	100 mmol/L	98-105 mmol/L
Urea	5.2 mmol/L	2.1-7.1 mmol/L
Creatinine	86 µmol/L	48-90 µmol/L
Calcium	2.2 mmol/L	2.15 - 2.5 mmol/L
Magnesium	0.97 mmol/L	0.63-1.05 mmol/L
Phosphate	0.91 mmol/L	0.78-1.42 mmol/L
C-reactive protein	17 mg/L	<10 mg/L
Erythrocyte sedimentation rate	12 mm/hr	0-10 mm/hr
Total protein	71 g/L	60 – 78 g/L
Total Bilirubin	11 µmol/L	5-21 µmol/L
Alkaline phosphatase	96 U/L	42-98 U/L
Aspartate transaminase	41 U/L	13-35 U/L
Alanine transaminase	27 U/L	7-35 U/L
Total cholesterol	3,3 mmol/L	<4,5 mmol/L
HbA1C	4.9%	<7%
INR	1	1
Rheumatoid factor	16 IU/L	<20 IU/L
Vitamin B12	166 pmol/L	145-569 pmol/L
Folate acid	30,5 nmol/L	
Thyroid stimulating hormone	1.01 MiU/L	0.27-4.2 MiU/l
Anticardiolipin antibody	negative	
Protein S	93 IU/dL	55-123 IU/dl
Protein C	121 IU/dl	70-130 IU/dL
Angiotensin-converting enzyme	222 IU/L	8-53 IU/L
Anticardiolipin antibody	negative	
Anti-streptolysin O titre	103 IU/ml	<200 IU/L
Ferritin	403 ng/mL	12 to 300 ng/mL
D-dimer	0.99 µg/ml	<0.50 mg/l (µg/ml=mg/l)
Elisa Cysticercosis	Positive	
AED LEVELS	All at therapeutic level	
PCR COVID-19	Positive	
POC COVID-19 antibody tests	Positive	
CSF: Cytology, chemistry, viral panel, ADA, NCC	Normal	

Comments: Patients presenting recurrent ES due to the dying process and no responding well to PZQ and PRE have been reported many times in our setting. Nonetheless, PZQ eliminates intraparenchymal solitary cyst in most cases. When the parasite is dying (colloid stage), some patient's present aggravation because of activation of the astrocytes and pro-inflammatory cytokine production [55]. Notwithstanding, NCC/Ep patients respond very well to Phenytoin (PHY), Carbamazepine (CBZ), or Valproic Acid (VA) to control their ES under normal circumstances [56-59]. In cases with associated SARS-CoV-2 infection, other precautions should be taken into consideration.

When COVID-19 is present, it is essential to consider that the Antiepileptic Drugs (AED) and Anti-Seizure Medications (ASM) can interact with other drugs used to treat COVID-19, such as favipiravir, remdesivir, lopinavir/ritonavir, tocilizumab, nitazoxanide chloroquine, interferon beta, hydroxychloroquine, and sofosbuvir. Unfortunately, the commonest AED/ASM used in endemic areas for NCC to treat ES/Ep (CBZ, PHY, phenobarbital, primidone, and VA) have significant drug interactions COVID-19 medications and those AED. Nevertheless, there is no significant drug interaction with gabapentin, pregabalin, levetiracetam, brivaracetam and vigabatrin, but unfortunately, these AED are not available in our rural areas and in most poor regions where taeniasis/cysticercosis is endemic

[60,61].

For NCC/Ep patients taking Lamotrigine (LMT) infected by SARS-CoV-2 and COVID-19 treatment, increasing its dosage to at least two times more than therapeutic dosage is recommended because lopinavir/ritonavir diminishes plasma concentration of LMT by induction of the glucuronidation enzyme system [62]. Patients are suffering TCGS and NCC with surrounding oedema plus COVID-19 infections will need higher doses of steroids (minimum 60 mg of prednisone daily) because SARS-CoV-2 infection causes a supplementary cytokine storm resulting in more disruption of the Blood-Brain Barrier (BBB) and more vasogenic oedema than the one caused by NCC solely. The colloid stage and the viral infection cause brain oedema. Therefore, we recommend additional acetazolamide 500 mg orally every 8 hours to decrease CSF production, mainly during the COVID-19 treatment, and keep AEDs at higher therapeutic levels to prevent SE with the consequent poor prognosis despite other authors treating patients with COVID-19/ES did not advise to manage the brain oedema [63,64].

One neuropathological factor to consider in managing NCC/COVID-19/ES/Ep is the brain's hypoxia on ES's mechanism. When the virus begins to replicate in the lung cells, it affects the alveolar gas exchange, and this process causes hypoxia of the CNS, causing accumulation of lactic acid, secondary cerebral vasodilation, brain oedema, swelling of the neurons, and blood flow disturbance leading to congestion and ischemia, which aggravates the patient's condition and increases the frequency of ES and SE [1]. Therefore, administering oxygen therapy is strongly recommended. Without a doubt, CBZ and lamotrigine are the medications of choice for treating partial simple or focal complex ES in developing countries [64,65], but they have an essential interaction with COVID-19 medicines [60,66]. Therefore, these AEDs should be used with caution.

Patients taking CBZ and ritonavir may complain of undesired side effects because ritonavir is a potent inhibitor of CYP3A/ CYP2D6 that increases CBZ plasma levels [66,67]. The administration of CBZ, PHY, PHE, or OXCBZ, together with fosbuvir, is expected to diminish the concentration of fosbuvir in blood [68]. The prognosis of COVID-19 patients with focal ES is worse compared with those without ES [69]. Below, we will discuss GI symptoms and associated depression in this case. An associated Cytokinetic Storm Syndrome (CSS) can be prevented if anti-parasitic medication to kill the parasites is not used until patient recovery from COVID-19 and IL-6 levels are normal.

Case 2: A 42-years-old lady with six years history of chronic headache, recurrent TCGS, no well-controlled plus NCC and poor compliance. The patient received VA 1 g orally twice a day, CBZ 400 mg BD orally and clonazepam 2 mg po nocte, and Albendazole 800 mg/day with 40 mg of PRE po daily for two weeks. Three months later patient came to NCC/Ep clinic in Nelson Mandela Academic Hospital in South Africa, presenting three days history of high fever, cough, abdominal pain, and diarrhoeas, waves of nausea, vomiting, generalized joint pains, and anosmia followed by two hours history of recurrent TCGS without recovery the expected level of consciousness between the ES. COVID test was positive, and the patient did not respond to lorazepam 4 mm intravenously twice. Then she transferred to ICU in established SE where she received propofol infusion Patient was in very critically ill condition no responding at the initial management with propofol and midazolam at the therapeutic dosage. However, two days later, she recovered from refractory SE and went back home on the seventh day of admission (Table 2).

Table 2. Components of cells and its cell count for case two.

Cells	Cell count	
White cell count	10.3 × 10 ⁹ /L	3.9-12,6 × 10 ⁹ /L
Hb	13.4 g/dL	12-15 g/dl
Platelets	301 × 10 ⁹ /L	186-454/L
Sodium	145 mmol/L	136–145 mmol/L
Potassium	5.0 mmol/L	3.5-5.1 mmol/L
Chloride	100 mmol/L	98-105 mmol/L
Urea	5.2 mmol/L	2.1-7.1 mmol/L

Creatinine	84 µmol/L	48-90 µmol/L
Calcium	2.4 mmol/L	2.15-2.5 mmol/L
Magnesium	0.81 mmol/L	0.63-1.05 mmol/L
Phosphate	0.80 mmol/L	0.78-1.42 mmol/L
C-reactive protein	10 mg/L	<10 mg/L
Erythrocyte sedimentation rate	12 mm/hr	0-10 mm/hr
Total protein	75 g/L	60-78 g/L
Total Bilirubin	8 µmol/L	5-21 µmol/L
Alkaline phosphatase	98 U/L	42-98 U/L
Aspartate transaminase	42 U/L	13-35 U/L
Alanine transaminase	24 U/L	7-35 U/L
Total cholesterol	3,9 mmol/L	<4,5 mmol/L
D-dimer	329 ng/ml	<250 ng/ml
Rheumatoid factor	17 IU/L	<20 IU/L
Vitamin B12	130 pmol/L	145-569 pmol/L
CSF	Normal	

Discussion

During the current pandemic, NCC complications remain to be emergencies, and a coordinated multidisciplinary team is necessary to provide the best management of NCC/COVID-19, which will reduce the functioning of select specialist units or general wards to prevent hospital cross-infection and patients treated by doctors with no experience in NCC. Even in countries with efficient healthcare systems reporting cases having an ES, SE, stroke, or other neurological disorder, they have no idea whether to attend a COVID centre or a general hospital and where to go for treatment due to the extant crisis [49]. Therefore, it is vital that each health centre, regional, or tertiary hospital has a separate screening area before the emergency triage.

From the previous coronaviruses pandemics, it is evident that all coronaviruses are neurotropic agents with a capacity to activate the CNS's supporting cells and provoke a pro-inflammatory state. Activated microglia by themselves may provide either short-term neuroprotection or decatenate long-term neurodegeneration according to the role played by the pro-and anti-inflammatory cytokines released in response to viral lesions. Resident brain glial cells can be transformed into dangerous and aggressive effector cells causing neuronal damage [50]. The elevated level of pro-inflammatory cytokines in serum can cause chronic inflammation and brain damage [1,51]. Apart from the information mentioned above, it is essential to consider that COVID-19 also binds to the brain's ACE-2 receptors, leading to impaired consciousness and seizures [8], increasing vascular complications and ultimately a high mortality rate.

At the beginning of the COVID-19 infection, increased secretion of inflammatory cytokines (IL-1 β , IFN- γ , TNF- α , IL-4, IL-6, IL-10) is seen. Furthermore, due to rapid viral replication and secondary cellular injury, some investigators have confirmed a relevant increase in the incidence of COVID-19 with ES [8,52,53]. The mortality rate of COVID-19 is 2.3% among the general population and 14.8% in older people (>80 years of age), and the comorbidity of NCC and COVID-19 deserves special attention to saving lives of the affected cases [54]. Refractory Ep is rare in patients with NCC [31-37,58,59,64,65], and SE represents the most severe presentation of Ep that usually occurs when patients discontinue AED (poor compliance) or when medications are not available due to COVID-19 restrictions, among other reasons including associated infections, metabolic disturbances, or electrolyte imbalance.

The Association of COVID-19 and SE is rare, and we only found six reported cases in our systematic literature review [13,23-25,45], but we did not find patients affected by NCC/COVID-19/SE together. The use of some ASM and anti-COVID medicines may cause undesirable complications [60]. Therefore, these medications must be used with caution as well. For example, lacosamide can control seizures in refractory SE, but it prolongs

the PR interval in the electrocardiogram, while hydroxychloroquine, azithromycin, phenytoin, carbamazepine, and rifinamide causes elongation of the QT interval leading to cardiac conduction disturbances [13,70]. Therefore, combining the mentioned ASM with hydroxychloroquine and azithromycin can be harmful. Therefore, we recommend performing the EKG monitoring routinely.

Fortunately, patients in the early-stage SE with or without NCC/COVID-19 should respond to Intravenous (IV) lorazepam or Intramuscular (IM) midazolam, and this ASM provides reasonable control of SE in approximately 63% -73% of patients without drugs interaction [71]. Notwithstanding benzodiazepines do not interact with COVID-19 medications, if the patient does not respond appropriately (like our case), then the medication for those patients (NCC with regular SE) may be intravenous PHY, or PHB usually happens. Because this AED/ASM have an essential interaction with COVID-19 medicines [60], they can be used cautiously at the loading dosage of 20 mg/kg, in the case of PHY (IV) at the range of 30 mg/min to avoid arrhythmias, mainly in COVID-19 cardiopathy. Unfortunately, there is no clinical trial conducted yet. Therefore, we cannot recommend the best choice for NCC/COVID-19/SE patients based on scientific evidence-based only on pharmacological action; IV-VA at the dosage of 30 mg/kg can be the right choice levetiracetam usually is not available in regions where NCC is endemic. Lacosamide (LCS) administration may develop atrial arrhythmias (atrial fibrillation or flutter) in patients with known heart conduction disturbances (sick sinus syndrome without pacemaker or AV block), Brugada syndrome (sodium channelopathy), ischemic heart disease, and diabetic polyneuropathy, among other COVID-19 cardiovascular diseases [72]. Considering that COVID-19 can develop cardiac problems by the virus's direct effect, there is no reason to administer LCS in patients with NCC/COVID-19/SE if another ASM is available.

For patients suffering from NCC/COVID-19/refractory SE, anaesthetics like midazolam, propofol, thiopental, and pentobarbital are good choices to be considered because they have no essential interaction with COVID-19 medicines. However, if NCC/COVID-19/SE patient continues having seizures after 24 hours of maximal dosage of IV anaesthetics in ICU (super refractory SE), the maximal dosage of IV corticosteroids is the treatment of choice. Although the prognosis is abysmal at this stage, combining IV magnesium and immunoglobulin can help save lives. Despite little evidence, the American Center for Disease Control and Prevention considers that some neurological comorbidity are risk factors for COVID-19, including epilepsy, but this consideration has not received unanimous support from the neuroscience community [73]. Moreover, based on past experiences with another infectious disease, an association has not been documented like other pre-existing comorbidities (such as cancer, diabetes, heart disease, obesity, smoking, and lung disease), recognized as risk factors [74,75].

Knowing that the Angiotensin-Converting Enzyme two (ACE-2) receptors have been found on the surface of neurons and glial cells, it makes sense to considering neuronal lesions caused by SARS-Cov-2 leads seizure disorder [76,77]. However, the prevalence of new-onset seizures disorder has not been confirmed [78], one therapeutic challenger right selection of the AED/ASM to be used in COVID-19 patients on antiretroviral therapy. To select the best medication, we recommend checking the Italian League against Epilepsy table, which contains updated information about interactions between antiretroviral medicines and AED. Another aspect to consider is the adequate management of COVID/Ep to decrease the risk of Sudden Unexpected Death in Epilepsy (SUDEP) secondary to COVID-19 [73]. Although no convincing data have been released up to date, taking a strict precaution on the best control of Es is strongly recommended. Other investigators reported that previously well-controlled epileptic patients during the COVID-19 pandemic probably developed recurrent seizures due to social isolation, quarantine, lack of physical activity, sedentary behaviours, and other changes in lifestyle combined with associated emotional stress and psychological disturbances [78]. Therefore, despite all limitations caused by the pandemic, these factors must be managed integrally to achieve successful results.

Recently have been proved that a direct invasion of the SARS-CoV-2 to the CNS is probably not the main cause of neurological manifestation because the lower concentrations of the virus found in the CSF and almost all neurological complications secondary to SARS-CoV-2 are not related to direct viral neuroinvasion [79]. Then other entries have been confirmed, and it seems to be that the disruption of the Blood-Brain-Barrier (BBB) is the main one by disassembly the tight junction (Tj) of the epithelial and endothelial barriers as specifically happens in severe COVID-19 cases [80-94]. As before-mentioned, SARS-CoV-2 use different routes to entry to the CNS, and one essential is the route from the intestine to the brain involving Toll-Like Receptor 4 (TLR4), zonulin (Zn), zonulin brain receptor and Protease-Activate Receptor 2 (PAR2) [95-99]. Zn is a 47 KDa protein that provides endogenous regulation of intestinal paracellular permeability by disassembling Tj [100-106]. This protein can be found in the GI tract, lungs, and CNS, augmenting the permeability of the BBB in the brain [107-110]. Another critical issue is the new AT-1001 (Zn peptide antagonist) which has been listed as a specific medication (Larazotide Acetate) against SARS-CoV-2 to combat COVID-19 more efficiently together with the AED or ASM, promising a better future for these patients [111].

The Role Played by Microbiota

The intestine in the mammalian host-microbial community comprises 1,000 or 1,500 bacterial species, known as "microbiota", and it comprises fungi, bacteria, yeasts, viruses, and bacteriophages. There is a closed relationship between the Gut Microbiota (GM) and the host characterized by a symbiotic mechanism with mutual benefits, including a well-organized immune system working in both directions through GM and the CNS via Gut-Microbiota-Brain axis (GMBa or MBA)) SARS-CoV-2 in neurons, glial cells, epithelial cells of the lungs, and Gastrointestinal System (GIs) is facilitated by Zonulin (Zn) and ACE2 receptors, which modulate the entry of the virus into cells. Thus, it explains the combination of GI, respiratory and neurological manifestations commonly seen in COVID patients like our cases.

The virus penetrates the Intestinal Epithelial Cells (IEC) from the intestinal lumen by ACE2 entrance receptor, affecting the homeostasis microbiota-mucosal immune function by decreased concentration of Lactobacillus and Bifidobacterium (also known by dysbiosis) via haematological route and retrograde afferent Vagal Nerve (VN) reperussing into the brain by super neuroinflammation (CS) and dysfunctional neuroimmunology leading to ischemic cerebrovascular disease, disorders of consciousness and ES [112-115].

Here it is essential to highlight that the source and maintenance of the mucosa-immune system are strongly related to the acquisition of a complex microbiota and its established symbiotic relationship. Therefore, dysfunction of this mechanism will cause allergic disorders, chronic inflammatory diseases, and autoimmune problems like mucosa pro-inflammatory response instead of autoimmune regulation plus microbial dysbiosis and CNS damage [116]. Other authors proved that the Gut-Brain Axis (GBA) has remarkable participation in the pathogenesis of MS, stroke, and Ep, as was seen in our series On the other hand, the presence of macrophage infiltrates, hypertrophic astrocytes (releasing cytokines, chemokines, and growth factors), and Perivascular-Activated Microglia (PAM) adjacent to neurons (neuronophagia) have been confirmed in the Dorsal Motor Nucleus (DMN) of VN, substantial nigra and pre-Böttinger complex (glycinergic neurons which inhibit respiratory activity) of MO, and olfactory bulb of COVID-19 cases. Some authors reported that these findings were involved in the production of spontaneous rhythmic breathing [117,118].

Role of astrocytes

Other viral infections (apart from SARS-CoV-2) and other CNS infections can trigger reactive astrogliosis, as shown in *Taenia solium* infections when the cysticercus is dying of natural causes or killed by medications [62], as we suspect in our first case. In this situation, Activated Astrocytes (AA) leads to local hyper inflammation due to CS and associated peripheral oedema. However, we do not believe that local reaction is strong enough

to provoke all clinical manifestations present in our patients. However, the associated SARS-CoV-2 infection with the virus's direct effect on the neurons and supporting cells supported by another mechanism such as Microbiota-Gut-Brain-Axis (MGBA) can explain recurrent ES, respiratory and GI manifestations, as will be discussed later in Figure 2. Other authors have mentioned the high susceptibility of SARS-CoV-2 to neurons, neural progenitor cells (brain organoids), glial cells beside Choroid Plexus Epithelial Cells (CPEC) [119]. As shown in Figure 2, the hematogenous route involves the CPEC, another wall block named Blood-Cerebrospinal-Barrier (BCB), one of the components of our first hypothesis explaining the pathogenesis of increased frequency of ES in our cases from NCC/SARS-CoV-2/MGBA. In our opinion, the inflammation caused by all these mechanisms leads to a dysfunctional neuronal membrane which facilitates the production of hypersynchronous discharge responsible for ES.

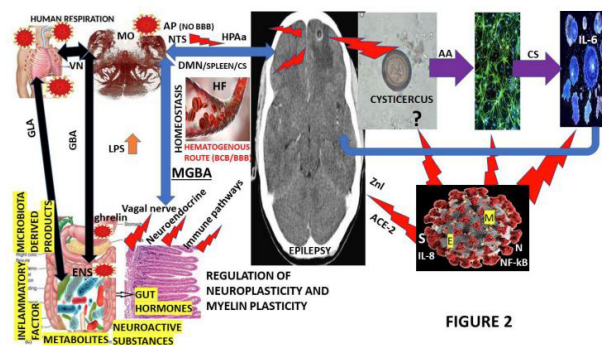


Figure 2. CT scan of the brain axial view: Showing a single cystic lesion in colloid state with surrounding oedema and pathogenesis of hypersynchronous discharge of cortical neurons (ES) in combination with role played by GM/ENS/MO/HPA, CRS, HF, disruption of BBB, SARS-CoV-2/CRS.

The AA, as mentioned earlier, can attract immune cells around to the focal lesion leading to immune cells infiltration and neuroinflammation with an associated epileptic focus. As it is well known, these AA increase releasing of chemokines/cytokines. These cytokines stimulate the innate neuronal immune response and neurotoxic elements, thus promoting brain damage apart from the brain damage caused through mechanisms from existing connections between the GI system and cognitive centres of the CNS in COVID-19 patients supported by GM and innate immunity activities. Recently, has been demonstrated that a group of astrocytes with anti-inflammatory properties may control the intensity of the CNS inflammation relayed by microbiome [120,121]. Our hypothesis to understand the circumscribed brain lesion despite the presence of two epileptogenic comorbidities is based on that announcement. Nonetheless, the astrocytes shape provides for homeostasis and CNS protection, supporting neuronal activities that can be affected by neurodegenerating-relate changes and ageing leading to asthenia, atrophy, and loss of function [122]. These alterations can aggravate the outcome of COVID-19 in patients presenting Alzheimer's disease and Ep, putting those cases with pre-existing diseases at an elevated risk of fatal COVID-19 outcome or higher risk of developing complications like SE, as happened in our second case.

Severe COVID-19 patients have been linked to a systemic inflammatory response (CS) characterized by a sharp increase level of pro-inflammatory cytokines, mainly IL-6, which is represented in Figures 2 and 3. AA's primary multifaceted physiological function in the CNS is highlighted as follows: 1.-Neurotrophic, 2.-Neuroprotected effect apart from demyelination, astrogliosis, and mediator of inflammation. Its expression is elevated during inflammation, injury, stroke, and infection [96], including viral and parasitic infection on the CNS causing ES/Ep.

On the other hand, some authors have confirmed that cases presenting intractable Ep also have Gut Microbiota (GM) dysbiosis represented by the lower amount of Bacteroidetes than an elevated Actinobacteria in healthy peoples. The same authors identified *Enterococcus faecium*, *Bifidobacterium longum*, and *Eggerthella lenta* as a biomarker for intractable Ep [115], represented in Figure 3. MB community leads high concentration of gamma-aminobutyric acid (inhibitory neurotransmitter)

and decreased glutamate (excitatory neurotransmitter) in the hippocampus [120]. Both neurotransmitters are strongly associated with ES suppression [123]. Apart from the evidence on GM dysbiosis and its etiopathogenic role in drug-resistant Ep, there is historical evidence from the effect of a ketogenic diet on GM composition alterations in better control medically refractory ES. Thus, seem to be that GM challenges CNS homeostasis, and modifications in the GM composition are linked to Ep, drug-resistant Ep (DRE) or medically refractory presentation from other causes and supported by others [124-128]. Therefore, therapeutic modifications of the GM composition (symbiotics) could be used as a novel treatment for DRE and other presentations of Ep as having been proposed by others if future clinical trials results confirm this hypothesis [129,130]. As is shown in Figure 3, the integrity and function of the GI tract are regulated by CNS through the endocrine HPA and ANS (represented in Figure 2), controlling the composition of GM, its motility, and secretory function. In the reverse pathway, the GI system affect the brain function, including behaviour and neuropsychiatric manifestations activating stress response mechanisms, increasing production of neurotransmitters, preserving the BBB integrity and promoting synaptogenesis; all these mechanisms by the mediation of the GM population supported by the emerging postulate of Microbiota-Gut-Brain-Axis (MGBA) as have been graphically represented in Figure 2 which include metabolic products from GM, ENS, ANS (parasympathetic and sympathetic branches), Neuroendocrine System (NES), Neural-Immune System (NIS), and CNS [131-136].

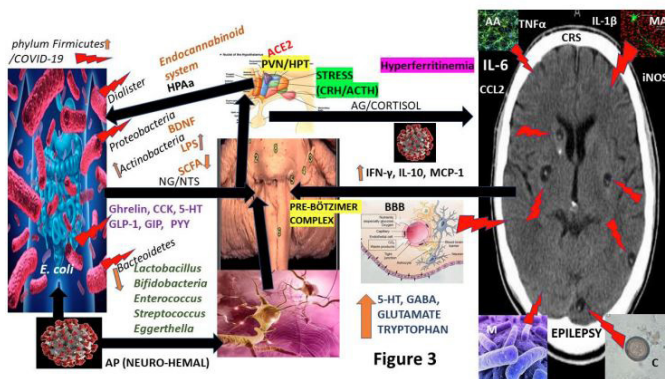


Figure 3. Axial view of CT brain scan shows multiple cysticerci lesions in vesicular and colloid state with excentric scolex, calcified NCC in the head of caudate nucleus and hypothesized mechanism of pathogenic ES/SE secondary to NCC/CRS, SARS-CoV-2/CRS, disruption of the BBB, HF, GM dysbiosis, enteric neurohormones dysfunction, neurotransmitters disorders and their pathways.

Mechanism of control by GM

Despite, there are several ways of communication as before-mentioned but in summary, can be grouped in five paths such as the neuroendocrine HPA axis, neural connections, the intestinal immune system, biosynthesis of neurotransmitters, and the interconnected BBB of the brain and the Intestinal Mucosa Barrier (IMB), while other pathophysiological pathways linking epileptogenesis and GM are still under investigations [137-139].

In Figure 3, we listed some neurotransmitters released by GM (5-HT, GABA, glutamate, tryptophan) as one mechanism involved in the direct action of the neural network [140,141], which modifies the balance between inhibition and excitation in the CNS. Neural signalling is another involved mechanism [137,139]. GM Excites Afferent Neurons (ENS) after VN stimulation inducing an anti-inflammatory response under homeostatic conditions [142-145].

Back to GM/ES/Ep is essential to highlight another solid pathogenetic mechanism triggering ES by GM are:

- Secondary neuroinflammation related to the biosynthesis of Short-Chain Fatty Acids (SCFA) [146].
- Disrupting the HPA axis [147].
- Modulating levels of BDNF (brain-derived neurotrophic factor) [147].

- Disrupting the endocannabinoid system linked to the pathogenesis of Ep [148,149].
- Causing a "Leakage" in the components of the BBB or intestinal mucosa barrier (IMB) [150].
- Increasing production of bacteria Lipopolysaccharide (LPS), which cause more permeability of IMB [141,151]. In addition, the LPS mediate upregulation of IL-1b, TNF and COX-2 (BBB and pro-inflammatory entry) [152].
- Modifying diet, increasing antibiotics, reducing symbiotics, Faecal Microbiota Transplantation (FMT) [150, 153-155].
- Promoting the direct cross-talk between GM and neurons and its impact on the brain cortex, leading to hypersynchrony neuronal discharge and consequents ES/Ep as represented in Figures 2 and 3 [156].

Here is relevant to comment on the role of associated stress in NCC/COVID-19 patients with GM dysbiosis leading to ES/Ep/SE and associated depress syndrome. As a general response to stress situations, the adrenal gland is activated via the HPA axis leading to overproduction of cortisol, as shown in Figure 3, which stimulates several CNS regions, including the hippocampus and amygdala, favouring the onset of symptoms of depression and anxiety [157].

Depression in our patient was characterized by loss of interest in daily activities, fatigue, and persistent feelings of sadness, which were probably from environmental and genetic factors secondary to stress. Depression is the most everyday psychiatric comorbidity in epileptic patients leading to an inferior quality of life and prognosis, affecting up to 62% of patients with Ep, although it remains undertreated and even underrecognized [158-162]. Depression has been reported as the commonest trigger for ES in Ep [163-166]. A high grade of CNS inflammation is associated with depression and Ep induced by ES, behavioural, physiological, and environmental stressors and stress/depression are linked by the immune system [167-172]. On the other hand, exposure to stress sensitizes the inflammatory mechanism to subsequent insults like ES, predisposing these patients to an associated depressive syndrome [173-175].

The terminology of neuroinflammation refers to an intense and transient inflammatory response in the CNS related to increased expression of inflammatory mediators such as chemokines, cytokines, prostaglandins, cell adhesion molecules, pro-inflammatory enzymes, prostaglandin-ethanolamides and gliosis due to an enhanced ES [158]. The same authors suggest that reducing neuroinflammation after SE then-forthcoming recurrent ES and severity of Ep will be reduced. Microglial Activation (MA) is also represented in Figure 3 due to acute stress is accompanied by monocytosis. Some authors support this enunciate, while another reported that migration of monocytes is facilitated by disruption of the BBB secondary to acute stress response/HPA-axis activation [176-179]. The most common triggering factor of ES is everyday stressful activities, according to many patients' opinions, and the chronic stress causes the elevated frequency of ES in dangerous situations like local, national, or international war conflict, natural disasters, terrorist attack and deadly pandemic times like the current one [164,180-186].

Interestingly, enhanced synaptic efficacy can be obtained after prolonged SE by new synaptic formation, neurogenesis, and axonal sprouting despite selective neuronal degeneration and neuroinflammation, how is suspected in case two [187]. After ES, there are AA and MA displaying modifications in morphology and metabolic reactions, which have been demonstrated by high intense immunohistochemical staining of ionized calcium-binding adapter molecule 1(Iba1) and Glial Fibrillary Acidic Protein (GFAP) around 20 years back [188,189]. These AA, MA, infiltrating peripheral immune cells and endothelial cells elaborate and release numerous protective factors during SE. Some of these elements represented in Figure 3 are IL-6, TNF α , IL-1 β , plus chemokine C-C motif ligands 2 and 3 [190]. The role of AM in patients with SE secondary to poor compliance and those related to NCC/COVID-19 and all mechanisms involved in its pathogenesis is quite relevant. First, it is crucial to recall two MA types: the classical microglia 1 (M1) phenotype and

the alternative microglia 2 (M2) phenotype. M1 is involved in the creation of a neurotoxic environment with the presence of pro-inflammatory mediators, while M2 promote tissue repairing and cells protection with the presence of neurotrophic factors and anti-inflammatory mediators, which support the complexity of M1/M2 (MA) in the brain of epileptic patients. In the acute phase (up to three days after SE), the primary function of MA is protective (at the site of the lesion), helping to clear cellular debris by phagocytosis; between five to twelve months after SE (chronic phase), this prolonged MA affect the recovery process due to associated neurotoxicity leading to recurrent ES as it was suspected in our series [191-193].

Apart from the damage on the BBB caused by NCC characterized by perilesional vasogenic oedema on the CT brain of case one, the BBB is also damaged by SARS-CoV-2 through the hematogenous route discussed before. On the other hand, ES also cause damage to BBB, which plays a crucial role in homeostasis in the CNS and is comprised of microglia, endothelial cells, pericytes and astrocytes plus infiltration of neutrophils and monocytes (peripheral immune cells) secondary to the extensive-expression of cytokine and chemokine signalling [194-197]. Probable this damage can be attenuated by potent anti-inflammatory therapy, among other medicines. Therefore, new investigations to provide more accurate aetiological diagnosis, including GM composition and new clinical trials with favourable results for patients with NCC/COVID/Ep/SE with or without depressive symptoms, are urgent unmet needs.

Apart from the extensive list of neurological disorders related to GM dysbiosis and the well-known intercommunication between the CNS/GIs through the ENS, EECs and the neurotransmitter produced by GM dysbiosis, it also causes mental health and psychiatric disorders such as bipolar disorder, OCP, SSD, PSD, ASD, anxiety, dementia and previously discussed depression which could get benefits from restoration of the GM therapy as well [198-202]. If GM dysbiosis is a contributing cause or a consequence of SARS-CoV-2 infection remains unclear, pharmacological treatment addressed to decrease GI permeability could be favourable for COVID-19 patients. Fortunately, the same prophylactic recommendations delivered to eradicate cysticercosis/taeniosis, including eliminating faecal-oral transmission route, environmental and water sanitation, can play a remarkable role for COVID-19 containment, mainly in developing countries [59].

One accurate way to assess the autonomic dysfunction due to the severity of COVID-19 is through Heart Rate Variability (HRV), which has been review by Pan. Recently, these investigators found a consistent trend with HRV in critically ill patients ($P < 0.05$), and those severe patients with not improved HRV parameters needed more time for recovering and clearance SARS-CoV-2 ($P < 0.05$) [203]. Several years ago, we proposed that fractal properties of HIV as a novel way assess the heartbeat regulation by the ANS and today, enough evidence indicates that HRV measurements can be utilized as a non-invasive predictor of severity and clinical outcome of COVID-19 cases and its suitability for monitoring therapeutic results. Before making final comments about some novel therapeutic approaches, we want to discuss Hyperferritinemia (HF) present in our series and represented in Figure 3 as part of the mechanism of pathogenesis of ES/Ep [204].

The first to remember that the term "Cytokine Release Syndrome" (CRS) refers to a severely over-reactive immune system that progresses in an unregulated manner. Second, recall that ferritin level serves as an inflammatory marker in CRS-related disorders and the autoimmune pathological process. It is commonly elevated in SLE and RA. The leading producer of ferritin is macrophages activated by pro-inflammatory cytokines [203,204]. Elevated ferritin level (pro-inflammatory molecule) in our series was also considered inducing the production of cytokines and chemokines, as reported by other authors [205,206].

Novel therapies

Tocilizumab (TZ) has been selected as a medication of choice to treat severe CRS (also known as CS) [206]. This humanized monoclonal antibody was used at the beginning to treat some haematological tumours for suppressing the CRS generated during the therapeutic process. It was

recommended to be combined because it can suppress the CRS while preserving its anti-tumour therapeutic accuracy [206]. Unfortunately, at the beginning of the SARS-CoV-2 pandemic, the beneficial effects of TZ were unknown. However, its efficacy is currently well recognized in cases with severe COVID-19 disease because TZ has an exceptional selectivity to act against IL-6 receptor and could decrease serum levels of ferritin, CRP, and fibrinogen, improving the clinical conditions of COVID-19 patients. Baricitinib (BT) has been recommended to treat patients with moderate COVID-19 and associated CRS, indicate hospital admission or respiratory distress. BT is a tyrosine-protein kinase inhibitor able to reduce the systemic inflammatory response (decrease cytokine production) and inhibit protein kinases preventing the assembly of intracellular viral particles [207].

Now it is available an interleukin-1 receptor, named anakinra, to be used as an anti-inflammatory treatment, which interdicts the activity of IL-1 alpha and IL-1 beta. Anakinra effectively acts against CS, while other investigators reported that a high dose of intravenous anakinra provides good sustainable response in COVID-19 patients presenting CRS with a remarkable reduction of ferritin, D-dimers, CRP, and PCT. Even though glucocorticoids have been used to treat COVID-19 cases because it inhibits cytokine production and immune cell activation some authors do not recommend its use due to suppression of the immune system and the capacity to clear coronaviruses what is more the pulmonary dysfunction and the development of osteonecrosis of hip and knee reported during 2003 SARS epidemic. Nevertheless, waiting for novel results for ongoing clinical trials on dexamethasone may be the best advice.

Another medication used in our case, such as vitamin D (natural immunoregulator) that reduce the production of Th1 cytokines, especially $\text{TNF}\alpha$ and $\text{IFN-}\gamma$, is alleviating CS among other functions; zinc supplement, which is crucial to the function and development of the immune system, and statins that provide a better prognosis reducing mortality rate in COVID-19 patients. All of them have been studied before this article; therefore, because of the limitation of space, we will not expend more time on their discussion. However, some comments about the role of intravenous immunoglobulin (IVIG) and ulinastatin could be of general interest. IVIG inhibit complement activation (overwhelming the Fc receptors), the differentiation of pathogenic Th1 and Th17 subsets, neutralizing pathogenic autoantibodies and blocking the production of pro-inflammatory cytokines (listed several times before). Furthermore, IVIG at the dose of 20 g/day has proved to diminish the use of ventilators, improve the 28-day survival of ICU COVID-19 patients, and provide fast recovery. Nonetheless, IVIG combined with hydroxychloroquine exhibited a high mortality rate in another study, probable due to an associate thrombosis. Our final comment about ulinastatin (protease inhibitor), which has proven to be efficient in reducing the generation of pro-inflammatory factors like IL-6, $\text{IFN-}\gamma$, $\text{TNF-}\alpha$, and increasing the production of anti-inflammatory factor IL-10 that provide an equilibrium between pro/anti-inflammatory response and protect the vascular endothelium leading to better capillary permeability. Ulinastatin reduces 28-day mortality in infected patients acutely. Now we have no idea when this pandemic will end despite the international vaccination programme. Fortunately, we know more about COVID-19 today than last year, but even now, to write this article, South Africa is going back to stage four again because of an increasing number of infected peoples by a new variant gamma SARS-CoV-2. Therefore, more investigations, including clinical trials, should be implemented to find better prophylactic measures and the best therapy for this deadly pandemic and stop its propagation.

Conclusion

We propose to assess NCC cases with COVID-19 symptoms using a predefined quick checklist for COVID19 risk and active disease as high priority, as is done with other Covid-19 presentations. An infection control team should screen all confirmed NCC patients presenting with clinical manifestations for the following list of symptoms and signs: ageusia, anosmia dyspnea, fever, headache, cough, chest pain, myalgias, vomiting, diarrhoea, seizures, stroke, or any other neurological manifestation. As mentioned before, NCC can be the cause of Ep and ES. On the other

hand, COVID-19 can lead to ES, and SE can follow uncontrolled recurrent seizures. In our opinion, SE in NCC patients during the COVID-19 pandemic have a multifactorial origin, including the inability of AED and poor compliance, and COVID-19 creates a susceptible environment in which the disease thrives; in other words, the new coronavirus acts as another trigger for SE in NCC patients. NCC's presence with extensive lesions can be an independent predictor of mortality in Covid-19 patients due to the superimposed damage caused by SARS-CoV-2 on the brain, apart from the detrimental immune response caused by Covid-19 despite the level of care received. Undoubtedly, the comorbidity of NCC and COVID-19 is real despite a small number of reported cases. We expect to see more published cases shortly because NCC/EP/ES/SE are not uncommon conditions. However, as the Covid-19 pandemic with its high mortality rate is far from being contained and health systems are still overwhelmed in several countries; thus, the scarcity in reports is understandable. In conclusion, although some evidence is available, well-designed large double-blinded randomized controlled trials in humans are needed further to elucidate the effect of FMT in neurological disorders. Finally, we have hypothesized (Figures 2 and 3) on the pathogenesis of ES and SE from the NCC/CRS, SARS-CoV-2/CRS including the role played by GM from the ENS (gut hormones, gut metabolites, inflammatory factors, neuroactive substances, and microbiota-derived products to the MO/HPA via MGBA in ES, Ep and associated depression, plus the mechanism of HF on the overall process.

Limitations

We stipulate that our study has several limitations. Firstly, most studies and reviews are either case reports or case series; only a few were observational cohort studies and no randomized controlled trials. Therefore, many of these studies are considered publications with relatively lower quality and reporting bias. We could not conduct a clinical trial or cross-sectional study because of the lack of confirmed patients willing to participate and the limitations of the pandemic.

Ethical Approval and Consent to Participate

The author performed this study under the patient's right established in the Declaration of Helsinki. Because we used retrospective radiographic material and no identification is revealed, the NMHA Ethical Committee (NMAHEC: F-2021-a09) granted an exemption from ethics approval. All information is available to the Editor on request.

Availability of Data and Materials

The data and material that support the findings of this study are available on reasonable request from the corresponding author.

Competing Interest

The author of this manuscript has any conflict of interest to disclose. The authors declare that they researched the absence of any commercial, non-financial or financial relationships construed as a potential conflict of interest.

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Patient Consent

We obtained written permission from all patients to write and publish this article and all included materials.

Potential Conflicts

The author declares that he researched the absence of any commercial or financial relationships construed as a potential conflict of interest. Therefore, no conflict of interest to disclose.

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Declaration of Anonymity

The author certifies that he did not reveal the names, initials, and other identity forms of the patients in this publication and complete anonymity are guaranteed.

Data Availability Statement

The data used to supports this study are available on reasonable request from the corresponding author.

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