Clin Schizophr Relat Psychoses
Volume 15:S5, 2021
Doi: 10.3371/CSRP.FH.121421

Clinical Schizophrenia & Related Psychoses

Review Article

Hybrid Open Access

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

Humberto Foyaca Sibat*

Department of Neurology, Nelson Mandela Academic Hospital and Walter Sisulu University, Mthatha, South Africa

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: Itestinal 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 Splenial 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 SARV-CoV-2 (known as 20H/501.V2, B1.351 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.

***Corresponding Author:** Humberto Foyaca Sibat, Department of Neurology, Nelson Mandela Academic Hospital and Walter Sisulu University, Walter Sisulu University, Mthatha, South Africa; E-mail: humbertofoyacasibat@gmail.com*

Received date: 23 November, 2021; **Accepted date:** 07 December, 2021; **Published date:** 14 December, 2021

[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].

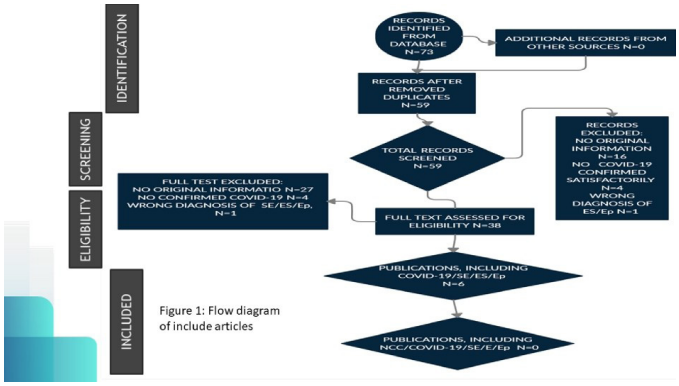

Figure 1. Flow diagram of included publications.

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 39th, 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 × 109/L	3.9-12,6 × 109/L
Hb	13.5 g/dL	12-15 g/dl
Platelets	291 × 109/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 umol/L	5-21 umol/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 ug/ml	<0.50 mg/l (ug/ml=mg/l)
Elisa Cysticercosis	Positive	
AED LEVELS	All at therapeutic level	
PCR COVID-19	Positve	
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 late 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 text 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 × 109/L	3.9-12,6 × 109/L
Hb	13.4 g/dL	12-15 g/dl
Platelets	301 × 109/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 umol/L	5-21 umol/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-1β, 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 unbalance.

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 rufinamide causes elongation of the QT interval leading to cardiac conduction disturbances [13,70]. Therefore, combiningTherefore, 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 (Znl), zonulin brain receptor and Protease-Activate Receptor 2 (PAR2) [95-99]. Znl 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, aumenting the permeability of the BBB in the brain [107-110]. Another critical issue is the new AT-1001 (Znl 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 (Znl) 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) repercussing 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-Bötzinger 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.

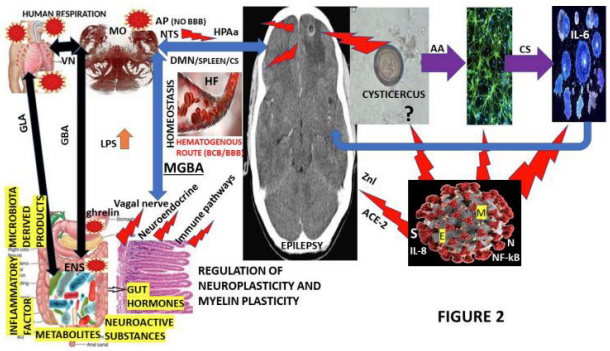

Figure 2. CT scan of the brain axial view: Showing a single cystic lesion in colloid state with surrounding oedema and pathogenesis of hypersynchronic discharge of cortical neurons (ES) in combination with role played by GM/ENS/MO/HPA, CRS, HF, disruption of BBB, SARS-Cov-2/CRS.

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].

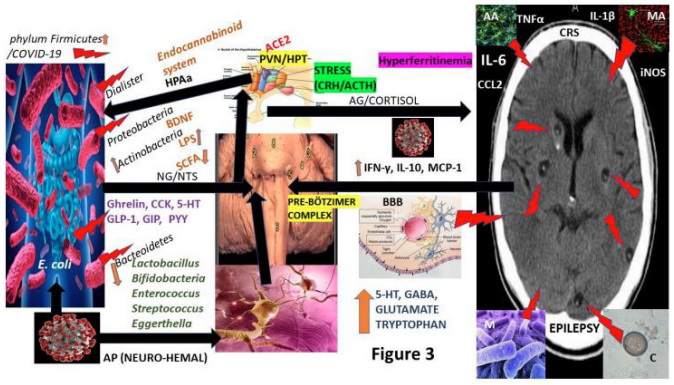

Figure 3

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 dusfuntion, 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 commonets 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 synapse 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, TNFα, IL-1β, 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 TNFα and IFN-γ, 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, IFN-γ, TNF-α, 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 manuscripy 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.

Funding

No financial support received. We declare no competing economic interests or personal relationships that could have influenced the work reported in this paper.

Authors' Information

HFS is an MD, MSc, PhD, First and Second degree specialist in Neurology, Full Professor (Cub), Associated Professor (WSU), Consultant Professor (Cub) and Ful Scientist Researcher, Full Scientist Research (Cub), HOD Neurology NMACH/WSU, Member of 15 International Medical Societies, Chief-Editor of IJN, member of CWGESA. Published many chapters and books on Epilepsy/NCC.

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.

Financial support: We declare no competing economic interests or personal relationships that could have influenced the work reported in this paper.

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.

Acknowledgement

Special thanks to Dr Lourdes de Fátima Ibañez Valdés from the Department of Radiology, NMACH. Mthatha, South Africa, for her support in the management of these patients.

References

1. Mao, Ling, Huijuan Jin, Mengdie Wang, and Yu Hu et al. "Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China." *JAMA Neurol* 77 (2020): 683-690.
2. Schwartz, David A, and Ashley L Graham. "Potential Maternal and Infant Outcomes from Coronavirus 2019-nCoV (SARS-CoV-2) Infecting Pregnant Women: Lessons from SARS, MERS, and Other Human Coronavirus Infections." *Viruses* 12 (2020): 194.
3. Ma, Ke, Tao Chen, MF Han, and Wei Guo, et al. "Management and clinical thinking of Coronavirus Disease 2019." *Chin J Hepatol* 28 (2020): E002-E002.
4. Nepal, Gaurav, Jessica Holly Rehrig, Gentle Sunder Shrestha and Yow Ka Shing, et al. "Neurological Manifestations of COVID-19: A Systematic Review." *Crit Care* 24 (2020): 1-11.
5. Pinzon, Rizaldy Taslim, Vincent Ongko Wijaya, Ranbebasa Bijak Buana, and Abraham Al Jody, et al. "Neurologic Characteristics in Coronavirus Disease 2019 (COVID-19): A Systematic Review and Meta-Analysis." *Front Neurol* 11 (2020): 565.
6. Hao, Xiaoting, Dong Zhou, Zhe Li and Guojun Zeng, et al. "Severe Psychological Distress among Patients with Epilepsy during the COVID-19 Outbreak in Southwest China." *Epilepsia* 61 (2020): 1166-1173.
7. Moriguchi, Takeshi, Norikazu Harii, Junko Goto, and Daiki Harada, et al. "A First Case of Meningitis/Encephalitis Associated with SARS-Coronavirus-2." *Int J Infect Dis* 94 (2020): 55-58.
8. Duong, Lisa, Prissilla Xu, and Antonio Liu. "Meningoencephalitis without Respiratory Failure in a Young Female Patient with COVID-19 Infection in Downtown Los Angeles, Early April 2020." *Brain Behav Immun* (2020).
9. Lu, Lu, Weixi Xiong, Dan Liu, and Jing Liu, et al. "New Onset Acute Symptomatic Seizure and Risk Factors in Coronavirus Disease 2019: A Retrospective Multicenter Study." *Epilepsia* 61 (2020): e49-e53.

10. Fasano, Antonio, Francesco Cavallieri, Elena Canali, and Franco Valzania. "First Motor Seizure as Presenting Symptom of SARS-CoV-2 Infection." *Neurol Sci* 41 (2020): 1651-1653.
11. Leonardi, Matilde, Alessandro Padovani, and Justin C McArthur. "Neurological Manifestations Associated with COVID-19: A Review and a Call for Action." *J Neurol* 267 (2020): 1573-1576.
12. Vollono, Catello, Eleonora Rollo, Marina Romozzi, and Giovanni Frisullo, et al. "Focal Status Epilepticus as Unique Clinical Feature of COVID-19: A Case Report." *Seizure* 78 (2020): 109-112.
13. Balloy, Gaëlle, Laurène Leclair-Visonneau, Yann Péréon, and Armelle Magot, et al. "Non-Lesional Status Epilepticus in a Patient with Coronavirus Disease 2019." *Clin Neurophysiol* 131 (2020): 2059-2061.
14. Somani, Sana, Sandipan Pati, Tyler Gaston, and Alissa Chitlangia, et al. "De Novo Status Epilepticus in Patients with COVID-19." *Ann Clin Transl Neurol* 7 (2020): 1240-1244.
15. Orsucci, Daniele, Elena Caldarazzo Ienco, Gianpaolo Nocita, and Alessandro Napolitano, et al. "Neurological Features of COVID-19 and their Treatment: A Review." *Drugs Context* (2020).
16. Ghannam, Malik, Qasem Alshaer, Mustafa Al-Chalabi, and Lara Zakarna, et al. "Neurological Involvement of Coronavirus Disease 2019: A Systematic Review." *J Neurol* 267 (2020): 3135-3153.
17. Gélisse, Philippe, Andrea O Rossetti, Pierre Genton, and Arielle Crespel, et al. "How to carry out and interpret EEG recordings in COVID-19 patients in ICU?." *Clin Neurophysiol* 131 (2020): 2023-2031.
18. Sheraton, Mack, Neha Deo, Rahul Kashyap, and Salim Surani. "A Review of Neurological Complications of COVID-19." *Cureus* 12 (2020).
19. Niazkar, Hamid Reza, Behdad Zibaee, Ali Nasimi, and Narjes Bahri. "The Neurological Manifestations of COVID-19: A Review Article." *Neurol Sci* 41 (2020): 1667-1671.
20. Gómez-Enjuto, Sara, Virgilio Hernando-Requejo, José Lapeña-Motilva, and Gonzalo Ogando-Durán, et al. "Verapamil as Treatment for Refractory Status Epilepticus Secondary to PRES Syndrome on a SARS-Cov-2 Infected Patient." *Seizure* 80 (2020): 157-158.
21. Abdulsalam, Mohammad A, Ahmad J Abdulsalam, and Diaa Shehab. "Generalized Status Epilepticus as a Possible Manifestation of COVID-19." *Acta Neurol Scand* (2020).
22. Kinney, Michael O., Francesco Brigo, and Peter W. Kaplan. "Optimizing Status Epilepticus care during the COVID-19 Pandemic." *Epilepsy Behav* 109 (2020).
23. Foyaca-Sibat, Humberto, Ibañez-Valdés LdeF, and J Moré-Rodríguez. "Parasitic Zoonoses of the Brain: Another Challenger." *Int J Neurol* 12 (2010): 9-14.
24. Foyaca-Sibat, Humberto, Linda D Cowan, Helene Carabin, and Irene Targonska, et al. "Accuracy of Serological Testing for the Diagnosis of Prevalent Neurocysticercosis in Outpatients with Epilepsy, Eastern Cape Province, South Africa." *PLoS Negl Trop Dis* 3 (2009): e562.
25. Sibat, Humberto Foyaca, and Lourdes de Fátima Ibañez Valdés. "Introduction to Cysticercosis and its Historical Background." *Novel Asp Cysticer Neurocys* (2013): 1.
26. Del Rio-Romero, AH, H Foyaca-Sibat, L de F Ibanez-Valdes, and E Vega-Novoa. "Prevalence of Epilepsy and General Knowledge about Neurocysticercosis at Nkalukeni Village, South Africa." *Int J Neurol* 3 (2005).
27. Humberto, Foyaca-Sibat, A Del Rio, Lourdes de Fátima Ibañez Valdés, and E Vega. "Neuroepidemiological Survey of Epilepsy and General Knowledge About Neurocysticercosis At Ngqwala Location, South Africa." *Int J Neurol* 3 (2004).
28. Foyaca-Sibat, H, A Del Rio-Romero, and L Ibanez-Valdes. "Prevalence of Epilepsy and General Knowledge about Neurocysticercosis at Ngangelizwe Location, South Africa." *Int J Neurol* 4 (2005).
29. Foyaca-Sibat, H, and RIA. Del Rio. "Epilepsy, Neurocysticercosis and, Poverty at Mphumaze and Marhambeni Locations, in South Africa." *Int J Neurol* 7 (2007): 8-14.
30. Del Rio, RA, H Foyaca-Sibat, and L Ibanez-Valdes. "Neuroepidemiological Survey for Epilepsy, Knowledge about Epilepsy, Neurocysticercosis and HIV/AIDS at the Makaula Village in South Africa." *Int J Neurol* 7 (2007).
31. Del Rio-Romero, AI, and H Foyaca-Sibat. "Ibañez-Valdés LdeF. "Neuroepidemiology findings as contributors for epilepsy due to neurocysticercosis at Mngceleni Location, South Africa." *Int J Neurol* 9 (2008): 33-40.
32. Foyaca-Sibat, H, and AI Del Rio-Romero. "Prevalence of Epilepsy in an Endemic Area for Neurocysticercosis in South Africa." *Int J Neurol* 9 (2008): 8-18.
33. Carabin, H., R. C. Krecek, L. D. Cowan, and L. Michael, et al. "Estimation of the Cost of Taenia Solium Cysticercosis in Eastern Cape Province, South Africa." *Trop Med Int Health* 11 (2006): 906-916.
34. "COVID-19 South African coronavirus news and information." (2021).
35. World Health Organization Coronavirus (COVID-2019) situation reports. "WHO Coronavirus (COVID-19) Dashboard." (2021).
36. Hung, Emily CW, Stephen SC Chim, Paul KS Chan, and Yu K Tong, et al. "Detection of SARS Coronavirus RNA in the Cerebrospinal Fluid of a Patient with Severe Acute Respiratory Syndrome." *Clin Chem* 49 (2003): 2108.
37. Lau, Kwok-Kwong, Wai-Cho Yu, Chung-Ming Chu, and Suet-Ting Lau, et al. "Possible Central Nervous System Infection by SARS Coronavirus." *Emerg Infect Dis* 10 (2004): 342.
38. Dominguez, Samuel R, Christine C Robinson, and Kathryn V. Holmes. "Detection of Four Human Coronaviruses in Respiratory Infections in Children: A One-Year Study in Colorado." *J Med Virol* 81 (2009): 1597-1604.
39. Swarz, Jeffrey A, Sarah Daily, Emily Niemi, and Samuel G Hilbert et al. "COVID-19 Infection Presenting as Acute-Onset Focal Status Epilepticus." *Pediatr Neurol* 112 (2020): 7.
40. McAbee, Gary N, Yuri Brosgol, Steven Pavlakis, and Rabia Agha, et al. "Encephalitis Associated with COVID-19 Infection in an 11-Year-Old Child." *Pediatr Neurol* 109 (2020): 94.
41. Pedersen, Savannah F, and Ya-Chi Ho. "SARS-CoV-2: A Storm is Raging." *J Clin Invest* 130 (2020): 2202-2205.
42. Wu, Yeshun, Xiaolin Xu, Zijun Chen, and Jiahao Duan, et al. "Nervous System Involvement after Infection with COVID-19 and Other Coronaviruses." *Brain Behav Immun* 87 (2020): 18-22.
43. Bhatia, Rohit, PN Sylaja, MV Padma Srivastava, and Dheeraj Khurana, et al. "Consensus Statement–Suggested Recommendations for Acute Stroke Management during the COVID-19 Pandemic: Expert Group on Behalf of the Indian Stroke Association." *Ann Indian Acad Neurol* 23 (2020): S15.
44. Lechien, Jerome R, Carlos M Chiesa-Estomba, Pierre Cabaraux, and Quentin Mat, et al. "Features of Mild-to-Moderate COVID-19 Patients with Dysphonia." *J Voice* (2020).
45. Jin, Huijuan, Candong Hong, Shengcai Chen, and Yifan Zhou et al. "Consensus for Prevention and Management of Coronavirus Disease 2019 (COVID-19) for Neurologists." *Stroke Vasc Neurol* 5 (2020).
46. Zhou, Fei, Ting Yu, Ronghui Du, and Guohui Fan et al. "Clinical Course and Risk Factors for Mortality of Adult Inpatients with COVID-19 in Wuhan, China: A Retrospective Cohort Study." *Lancet* 395 (2020): 1054-1062.
47. Poyiadji, Neo, Gassan Shahin, Daniel Noujaim, and Michael Stone, et al. "COVID-19–Associated Acute Hemorrhagic Necrotizing Encephalopathy: Imaging Features." *Radiology* 296 (2020): E119-E120.
48. Wu, Zunyou, and Jennifer M McGoogan. "Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases from the Chinese Center for Disease Control and Prevention." *JAMA* 323 (2020): 1239-1242.
49. Foyaca-Sibat, H and Ibañez-Valdés LdeF. "Clinical Trial of Praziquantel and Prednisone in Rural Patients with Neurocysticercosis Presenting Recurrent Epileptic Attacks." *Int J Neurol* 2 (2002): 41-50.
50. Foyaca-Sibat, H, and Ibañez-Valdés LdeF. "Pseudoseizures and Epilepsy in Neurocysticercosis." *Electron J Biomed* 2 (2003): 20-29.
51. Humberto, Foyaca-Sibat, Lourdes de Fátima Ibañez Valdés. "Pseudoseizures and Epilepsy in Neurocysticercosis: Some Advice for Family Doctors." *Int J Neurol* 2 (2003).
52. Foyaca-Sibat, Humberto, and Lourdes de Fátima Ibañez-Valdés. "Treatment of Epilepsy Secondary to Neurocysticercosis." *Novel Treatment of Epilepsy* (2011): 213.
53. Humberto, Foyaca-Sibat. "Epilepsy Secondary to Parasitic Zoonoses of the Brain." Novel Aspects on Epilepsy (2011).
54. Asadi-Pooya, Ali A, Armin Attar, Mohsen Moghadami, and Iman Karimzadeh. "Management of COVID-19 in People with Epilepsy: Drug Considerations." *Neurol Sci* (2020): 1-7.

55. Van der Lee, Manon J, Lara Dawood, Hadewych JM ter Hofstede, and Marga JA de Graaff-Teulen, et al. "Lopinavir/Ritonavir Reduces Lamotrigine Plasma Concentrations in Healthy Subjects." *Clin Pharmacol Ther* 80 (2006): 159-168.
56. Sibat, Humberto Foyaca, and LF Valdés. "Uncommon Clinical Manifestations of Cysticercosis." *Novel Asp Cystic Neuro* 8 (2013): 199-233.
57. Asadi-Pooya, A.A. "Seizures associated with Coronavirus Infections." *Seizure* 79 (2020): 49-52.
58. Asadi-Pooya, Ali A., and Michael R. Sperling. "Antiepileptic Drugs: A Clinician's Manual." *Oxford University Press* (2016).
59. Nguyen, Thai, Ian McNicholl, Joseph M Custodio, and Javier Szwarcberg et al. "Drug Interactions with Cobicistat-or Ritonavir-Boosted Elvitegravir." *AIDS reviews* 18 (2016): 101-111.
60. Trinka, Eugen, Julia Höfler, Markus Leitinger, and Francesco Brigo. "Pharmacotherapy for Status Epilepticus." *Drugs* 75 (2015): 1499-1521.
61. Huang, Chin-Wei W, Suzan Brown, Neelan Pillay, and Martin Del Campo, et al. "Electroencephalographic and Electrocardiographic Effect of Intravenous Lacosamide in Refractory Focal Epilepsy." *J Clin Neurophysiol* 35 (2018): 365-369.
62. Kuroda, Naoto. "Epilepsy and COVID-19: Associations and Important Considerations." *Epilepsy Behav* 108 (2020).
63. Jordan, Rachel E., Peymane Adab, and KK Cheng. "Covid-19: Risk Factors for Severe Disease and Death." *BMJ* (2020).
64. Li, Yan-Chao, Wan-Zhu Bai, and Tsutomu Hashikawa. "The Neuroinvasive Potential of SARS-CoV2 may Play a Role in the Respiratory Failure of COVID-19 Patients." *J Med Virol* 92 (2020): 552-555.
65. Baig, Abdul Mannan, Areeba Khaleeq, Usman Ali, and Hira Syeda. "Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host–Virus Interaction, and Proposed Neurotropic Mechanisms." *ACS Chem Nerosci* 11 (2020): 995-998.
66. Vancini, Rodrigo Luiz, Claudio Andre Barbosa de Lira, Marília Santos Andrade, and Ricardo Mário Arida. "CoVID-19 *vs.* Epilepsy: It is Time to Move, Act, and Encourage Physical Exercise." *Epilepsy Behav* 110 (2020): 107154.
67. Lewis, Ariane, Jennifer Frontera, Dimitris G. Placantonakis, and Jennifer Lighter, et al. "Cerebrospinal Fluid in COVID-19: A systematic Review of the Literature." *J Neurol Sci* (2021): 117316.
68. Uversky, Vladimir N, Fatma Elrashdy, Abdullah Aljadawi, and Syed Moasfar Ali, et al. "Severe Acute Respiratory Syndrome Coronavirus 2 Infection Reaches the Human Nervous System: How?." *J Neurosci Res* 99 (2021): 750-777.
69. Buzhdygan, Tetyana P, Brandon J DeOre, Abigail Baldwin-Leclair, and Trent A Bullock, et al. "The SARS-CoV-2 Spike Protein Alters Barrier Function in 2D Static and 3D Microfluidic In-Vitro Models of the Human Blood–Brain Barrier." *Neurobiol Dis* 146 (2020): 105131.
70. Wang, Wenle, Sergio Uzzau, Simeon E Goldblum, and Alessio Fasano. "Human Zonulin, a Potential Modulator of Intestinal Tight Junctions." *J Cell Sci* 113 (2000): 4435-4440.
71. Alquisiras-Burgos, Iván, Irlanda Peralta-Arrieta, Luis Antonio Alonso-Palomares, and Ana Elvira Zacapala-Gómez, et al. "Neurological Complications Associated with the Blood-Brain Barrier Damage Induced by the Inflammatory Response during SARS-CoV-2 Infection." *Mol Neurobiol* 58 (2021): 520-535.
72. Achar, Aneesha, and Chaitali Ghosh. "COVID-19-Associated Neurological Disorders: The Potential Route of CNS Invasion and Blood-Brain Barrier Relevance." *Cells* 9 (2020): 2360.
73. Xiao, Minjia, Zhi Jie Xiao, Binbin Yang, and Ziwei Lan, et al. "Blood-brain barrier: more contributor to disruption of central nervous system homeostasis than victim in neurological disorders." *Front Neurosci* 14 (2020): 14: 764.
74. Erickson, Michelle A, Elizabeth M Rhea, Rachel C Knopp and William A Banks. "Interactions of SARS-CoV-2 with the Blood–Brain Barrier." I*nt J Mol Sci* 22(2021): 2681.
75. Vargas, Gabriele, Luiz Henrique Medeiros Geraldo, Natália Salomão and Marciano Vianna Paes, et al. "Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and glial cells: Insights and perspectives." *Brain Behav Immun* (2020): 100127.
76. Burks, Susan M, Hector Rosas-Hernandez, Manuel Alenjandro Ramirez-Lee and Elvis Cuevas, et al. "Can SARS-CoV-2 infect the central nervous system *via* the olfactory bulb or the blood-brain barrier?." *Brain Behav Immun* (2021): 7-14.
77. Goldblum, Simeon E, Usha Rai, Amit Tripathi and Manjusha Thakar, et al. "The active Zot domain (aa 288–293) increases ZO-1 and myosin 1C serine/threonine phosphorylation, alters interaction between ZO-1 and its binding partners, and induces tight junction disassembly through proteinase activated receptor 2 activation." *FASEB J* 25(2011): 144-158.
78. Rittirsch, Daniel, Michael A Flierl, Brian A Nadeau and Danielle E Day, et al. "Zonulin as prehaptoglobin2 regulates lung permeability and activates the complement system." *Am J Physiol Lung Cell Mol Physiol* 304(2013): L863-L872.
79. Skardelly, Marco, Franz Paul Armbruster, Jürgen Meixensberger and Heidegard Hilbig. "Expression of zonulin, c-kit, and glial fibrillary acidic protein in human gliomas." *Transl Oncol* 2(2009): 117-120.
80. Lu, R, W Wang, S Uzzau and R Vigorito, et al. "Affinity purification and partial characterization of the zonulin/zonula occludens toxin (Zot) receptor from human brain." *J Neurochem* 74(2000): 320-326.
81. Bullen, C Korin, Helena T Hogberg, Asli Bahadirli-Talbott and William R Bishai, et al. "Infectability of human BrainSphere neurons suggests neurotropism of SARS-CoV-2." *ALTEX* 37(2020): 665-671.
82. Yachou, Yassine, Abdeslem El Idrissi, Vladimir Belapasov, and Said Ait Benali "Neuroinvasion, Neurotropic, and Neuroinflammatory Events of Sars-Cov-2: Understanding the Neurological Manifestations in COVID-19 Patients." *Neuro. Sci* 41 (2020): 1-13.
83. Murta, Veronica, Alejandro Villarreal, and Alberto J Ramos. "Severe Acute Respiratory Syndrome Coronavirus 2 Impact on the Central Nervous System: Are Astrocytes And Microglia Main Players Or Merely Bystanders?" *ASN neuro* 12 (2020): 1759091420954960.
84. Whittaker, Abigail, Matthew Anson, and Amer Harky. "Neurological Manifestations of COVID-19: A Systematic Review and Current Update." *Clin Neurol Neurosurg* 142 (2020): 14-22.
85. Pellegrini, Laura, Anna Albecka, Donna L. Mallery, and Max J. Kellner, et al. "SARS-CoV-2 Infects The Brain Choroid Plexus and Disrupts the Blood-Csf Barrier in Human Brain Organoids." *Cell stem cell* 27 (2020): 951-961.
86. Colombo E, Farina C. "Astrocytes: Key Regulators of Neuro Inflammation." *Trends Immunol* 37 (2016): 608-620.
87. Läubli, Heinz, and Ajit Varki. "Sialic Acid–Binding Immunoglobulin-Like Lectins (Siglecs) Detect Self-Associated Molecular Patterns To Regulate Immune Responses." *Cell Mol Life Sci* 77 (2020): 593-605.
88. Shinu, Pottathil, Mohamed A. Morsy, Pran Kishore Deb, and Anroop B Nair, et.al "SARS CoV-2 Organotropism Associated Pathogenic Relationship of Gut-Brain Axis and Illness." *Front Mol Biosci* 7 (2020): 432-439.
89. Andrade, Marileia Chaves, Rodolfo Souza de Faria, and Sergio Avelino Mota Nobre. "COVID-19: Can the symptomatic SARS-CoV-2 Infection Affect The Homeostasis Of The Gut-Brain-Microbiota Axis?" *Med Hypotheses* 144 (2020): 110206.
90. Ahlawat, Shruti, and Krishna Kant Sharma. "Immunological Co-Ordination between Gut and Lungs in SARS-CoV-2 Infection." *Virus Res* 286 (2020): 198103.
91. Di Micco, Simone, Simona Musella, Maria C. Scala, and Marina Sala, et.al. "In silico Analysis Revealed Potential Anti-SARS-CoV-2 Main Protease Activity by the Zonulin Inhibitor Larazotide Acetate." *Front Chem* 8 (2021): 1268-1271.
92. Sanmarco, Liliana M, Michael A. Wheeler, Cristina Gutiérrez-Vázquez, and Carolina Manganeli Polonio, et.al. "Gut-Licensed Ifnγ+ Nk Cells Drive Lamp1+ Trail+ Anti-Inflammatory Astrocytes." *Nature* 590 (2021): 473-479.
93. Verkhratsky, Alexei, Vladimir Parpura, Jose Julio Rodriguez-Arellano, and Robert Zorec. "Astroglia in Alzheimer's Disease." *Adv Exp Med Biol* 1175 (2019): 273-324.
94. Verkhratsky, Alexei, Marcus Augusto-Oliveira, Augustas Pivoriūnas, and Alexander Popov, et.al. "Astroglial Asthenia And Loss Of Function, Rather Than Reactivity, Contribute To The Ageing Of The Brain." *Pflugers Arch* 473 (2021): 753-774.
95. Lee, Kihyun, Namil Kim, Jung Ok Shim, and Gun-Ha Kim. "Gut Bacterial Dysbiosis In Children With Intractable Epilepsy." J Clin Med 10 (2021): 1-5.
96. Dahlin, Maria, and Stefanie Prast-Nielsen. "The Gut Microbiome and Epilepsy." *E Bio Medicine* 44 (2019): 741-746.

97. Sutter, Raoul, Stephan Rüegg, and Sarah Tschudin-Sutter. "Seizures As Adverse Events Of Antibiotic Drugs: A Systematic Review." *Neurology* 85 (2015): 1332-1341.

98. Becattini, Simone, Ying Taur, and Eric G. Pamer. "Antibiotic-Induced Changes in the Intestinal Microbiota and Disease." *Trends Mol Med* 22 (2016): 458-478.

99. He, Zhi, Bo-Ta Cui, Ting Zhang, and, Pan Li, et.al. "Fecal Microbiota Transplantation Cured Epilepsy in a Case with Crohn's Disease: The First Report." *World J Gastroenterol* 23 (2017): 3565–3568.

100. Carabotti, Marilia, Annunziata Scirocco, Maria Antonietta Maselli, and Carola Severi. "The Gut-Brain Axis: Interactions between Enteric Microbiota, Central and Enteric Nervous Systems." *Ann Gastroenterol* 28 (2015): 203-209.

101. Zuckerkandl, Emile, and Linus Pauling. "Evolutionary Divergence and Convergence In Proteins." *Science* 1 (1965): 97-166.

102. Maier, Len, Mett Pruteanu, Met Kuhn, and, G.Zeller, et.al. "Extensive Impact of Non-Antibiotic Drugs on Human Gut Bacteria." *Nature* 555(2018): 623-628.

103. Chatzikonstantinou, Simela, Georgia Gioula, Vasilios K. Kimiskidis, and Jack McKenna, et.al. "The Gut Microbiome in Drug-Resistant Epilepsy." *Epilepsia Open* 6 (2021): 28-37.

104. Lum, Gregory R, Christine A. Olson, and Elaine Y. Hsiao. "Emerging Roles for the Intestinal Microbiome in Epilepsy." *Neurobiol Dis* 135 (2020): 104576.

105. Song, Eun-Ji, Eun-Sook Lee, and Young-Do Nam. "Progress of Analytical Tools and Techniques for Human Gut Microbiome Research." *J Microbiol* 56 (2018): 693-705.

106. Mooser, Catherine, Mercedes Gomez de Agüero, and Stephanie C. Ganal-Vonarburg. "Standardization in Host–Microbiota Interaction Studies: Challenges, Gnotobiology as a Tool, and Perspective." *Curr Opin Microbiol* 44 (2018): 50-60.

107. De Caro, Carmen, Luigi Francesco Iannone, Rita Citraro, and Pasquale Striano, et.al. "Can We'Seize'the Gut Microbiota to Treat Epilepsy?" *Neurosci Biobehav Rev* 107 (2019): 750-764.

108. Holmes, Manisha, Zia Flaminio, Mridula Vardhan, and Fangxi Xu, et.al "Cross Talk between Drug-Resistant Epilepsy and the Gut Microbiome." *Epilepsia* 61 (2020): 2619-2628.

109. Cryan, John F, and Timothy G. Dinan. "Mind-Altering Microorganisms: The Impact of the Gut Microbiota On Brain and Behaviour." *Nat Rev Neurosci* 13 (2012): 701-712.

110. Mayer, Emeran A, Rob Knight, Sarkis K. Mazmanian, and John F. Cryan. "Gut Microbes and the Brain: Paradigm Shift in Neuroscience." *J Neurosci* 34 (2014): 15490-15496.

111. Smith, Peter Andrey. "The Tantalizing Links between Gut Microbes and the Brain." *Nature* 526 (2015): 312-314.

112. Schmidt, Charles. "Thinking From the Gut." *Nature* 518 (2015): S12-S14.

113. Mayer, Emeran A, Kirsten Tillisch, and Arpana Gupta. "Gut/Brain Axis and the Microbiota." *J Clin Invest* 125 (2015): 926-938.

114. Wang, Hong-Xing, and Yu-Ping Wang. "Gut Microbiota-Brain Axis." *Chin Med J* (Engl)129 (2016): 2373–2380.

115. Dinan, Timothy G, and John F. Cryan. "Brain–Gut–Microbiota Axis—Mood, Metabolism and Behaviour." *Nat Rev Gastroenterol Hepatol* 14 (2017): 69-70.

116. Foster, Jane A, Linda Rinaman, and John F. Cryan. "Stress and the Gut-Brain Axis: Regulation by the Microbiome." *Neurobiol Stress* 7 (2017): 124-136.

117. Warner, Barbara B. "The Contribution of the Gut Microbiome to Neurodevelopment and Neuropsychiatric Disorders." *Pediatr Res* 85 (2019): 216-224.

118. Bravo, Javier A, Paul Forsythe, Marianne V. Chew, and Emily Escaravage, et al. "Ingestion of Lactobacillus Strain Regulates Emotional Behavior and Central Gaba Receptor Expression In a Mouse *Via* The Vagus Nerve." *Proc Natl Acad Sci* 108 (2011): 16050-16055.

119. O'Mahony, Siobhain M, Gerard Clarke, YE Borre, and Tig G. Dinan, et al. "Serotonin, Tryptophan Metabolism and the Brain-Gut-Microbiome Axis." *Behav Brain Res* 277 (2015): 32-48.

120. Blander, J Magarian, Randy S Longman, Iliyan D. Iliev, and Gregory F Sonnenberg, "Regulation of Inflammation by Microbiota Interactions with the Host." *Nat Immunol* 18 (2017): 851-860.

121. Tognini, Paola. "Gut Microbiota: A Potential Regulator of Neurodevelopment." *Front Cell Neurosci* 11 (2017): 25-28.

122. Quigley, Eamonn MM. "Microbiota-Brain-Gut Axis and Neurodegenerative Diseases." *Curr Neurol Neurosci. Rep*. 17 (2017): 1-9.

123. Zhao, Zhen-Xiong, Jie Fu, Shu-Rong Ma, and Ran Peng, et al. "Gut-Brain Axis Metabolic Pathway Regulates Antidepressant Efficacy of Albiflorin." *Theranostics* 8 (2018): 5945-5959.

124. Van de Wouw, Marcel, Marcus Boehme, Joshua M. Lyte, and Niamh Wiley, et.al "Short-Chain Fatty Acids: Microbial Metabolites that Alleviate Stress-Induced Brain–Gut Axis Alterations." *J Physiol* 596 (2018): 4923-4944.

125. Sudo, Nobuyuki, Yoichi Chida, Yuji Aiba, and Junko Sonoda, et.al. "Postnatal Microbial Colonization Programs the Hypothalamic–Pituitary–Adrenal System For Stress Response In Mice." *J Physiol* 558 (2004): 263-275.

126. Al-Ghezi, Zinah Zamil, Philip Brandon Busbee, Hasan Alghetaa, and Prakash S. Nagarkatti. "Combination Of Cannabinoids, Delta-9-Tetrahydrocannabinol (Thc) And Cannabidiol (Cbd), Mitigates Experimental Autoimmune Encephalomyelitis (Eae) by Altering The Gut Microbiome." *Brain Behav Immun* 82 (2019): 25-35.

127. Mehrpouya-Bahrami, Pegah, Kumaraswamy Naidu Chitrala, Mitra S. Ganewatta, and Chuanbing Tang, et.al. "Blockade Of Cb1 Cannabinoid Receptor Alters Gut Microbiota and Attenuates Inflammation And Diet-Induced Obesity." *Sci Rep* 7 (2017): 1-16.

128. Balosso, Silvia, Jaron Liu, Marco E Bianchi and Annamaria Vezzani. "Disulfide-Containing High Mobility Group Box-1 Promotes N-Methyl-D-Aspartate Receptor Function and Excitotoxicity by Activating Toll-Like Receptor 4-Dependent Signaling in Hippocampal Neurons." *Antioxid Redox Signal* 21 (2014): 1726-1740.

129. Maroso, Mattia, Silvia Balosso, Teresa Ravizza and Jaron Liu, et al. "Toll-Like Receptor 4 and High-Mobility Group Box-1 Are Involved in Ictogenesis and Can Be Targeted To Reduce Seizures." *Nat Med* 16 (2010): 413-419.

130. Braakman, Hilde MH, and Jakko van Ingen. "Can Epilepsy Be Treated by Antibiotics?." *J Neurol* 265 (2018): 1934-1936.

131. Gómez-Eguílaz, M, J L Ramón-Trapero, L Pérez-Martínez, and J R Blanco. "The Beneficial Effect of Probiotics as a Supplementary Treatment in Drug-Resistant Epilepsy: A Pilot Study." *Benef Microbes* 9 (2018): 875-881.

132. Maiuolo, Jessica, Micaela Gliozzi, Vincenzo Musolino and Cristina Carresi, et al. "The Contribution of Gut Microbiota–Brain Axis in the Development of Brain Disorders." *Front Neurosci* 15 (2021): 616883.

133. Fiksdal, Alexander, Luke Hanlin, Yuliya Kuras and Danielle Gianferante, et al. "Associations Between Symptoms of Depression and Anxiety and Cortisol Responses to and Recovery From Acute Stress." *Psychoneuroendocrinol* 102 (2019): 44-52.

134. Espinosa-Garcia, Claudia, Helena Zeleke, and Asheebo Rojas. "Impact of Stress on Epilepsy: Focus on Neuroinflammation—A Mini Review." *Int J Mol Sci* 22 (2021): 4061.

135. Kanner, Andres M, and Antoaneta Balabanov. "Depression and Epilepsy: How Closely Related Are They?." *Neurology* 58 (2002): S27-S39.

136. Błaszczyk, Barbara, and Stanisław J. Czuczwar. "Epilepsy Coexisting With Depression." *Pharmacol Rep* 68 (2016): 1084-1092.

137. Elger, Christian E., Samantha A. Johnston, and Christian Hoppe. "Diagnosing and Treating Depression in Epilepsy." *Seizure* 44 (2017): 184-193.

138. Bermeo-Ovalle, Adriana. "Psychiatric Comorbidities Go Untreated in Patients With Epilepsy: Ignorance or Denial?." *Epilepsy Behav* 98 (2019): 306-308.

139. Temkin, Nancy R, and Gay R Davis. "Stress as a Risk Factor for Seizures Among Adults With Epilepsy." *Epilepsia* 25 (1984): 450-456.

140. Novakova, Barbora, Peter R Harris, Athi Ponnusamy and Markus Reuber. "The Role of Stress as a Trigger for Epileptic Seizures: A Narrative Review of Evidence From Human and Animal Studies." *Epilepsia* 54 (2013): 1866-1876.

141. McKee, Heather R, and Michael D Privitera. "Stress as a Seizure Precipitant: Identification, Associated Factors, and Treatment Options." *Seizure* 44 (2017): 21-26.

142. Lang, Johannes D, David C Taylor, and Burkhard S Kasper. "Stress, Seizures, and Epilepsy: Patient Narratives." *Epilepsy Behav* 80 (2018): 163-172.

143. Mazarati, Andrey M, Megan L Lewis, and Quentin J Pittman. "Neurobehavioral Comorbidities of Epilepsy: Role of Inflammation." *Epilepsia* 58 (2017): 48-56.

144. Slavich, George M, and Michael R Irwin. "From Stress to Inflammation and Major Depressive Disorder: A Social Signal Transduction Theory of Depression." *Psychol Bull* 140 (2014): 774-815.

145. Miller, Andrew H, and Charles L Raison. "The Role of Inflammation in Depression: From Evolutionary Imperative to Modern Treatment Target." *Nat Rev Immunol* 16 (2016): 22-34.

146. Ménard, Caroline, Madeline L Pfau, Georgia E Hodes and Scott J Russo. "Immune and Neuroendocrine Mechanisms of Stress Vulnerability and Resilience." *Neuropsychopharmacol* 42 (2017): 62-80.

147. Paudel, Yam Nath, Mohd Farooq Shaikh, Sadia Shah and Yatinesh Kumari, et al. "Role of Inflammation in Epilepsy and Neurobehavioral Comorbidities: Implication for Therapy." *Eur J Pharmacol* 837 (2018): 145-155.

148. Hayley, Shawn, Antoine M Hakim and Paul R Albert. "Depression, Dementia and Immune Dysregulation." *Brain* 144 (2021): 746-760.

149. Maguire, Jamie. "Primed for Problems: Stress Confers Vulnerability to Epilepsy and Associated Comorbidities: Stress Confers Vulnerability to Epilepsy and Associated Comorbidities." *Epilepsy Curr* 15 (2015): 344-346.

150. Frank, Matthew G, Michael D Weber, Linda R Watkins and Steven F Maier. "Stress-Induced Neuroinflammatory Priming: A Liability Factor in the Etiology of Psychiatric Disorders." *Neuro biol Stress* 4 (2016): 62-70.

151. Becker, Christel, Elodie Bouvier, Antoine Ghestem and Safia Siyoucef, et al. "Predicting and Treating Stress-Induced Vulnerability to Epilepsy and Depression." *Ann Neurol* 78 (2015): 128-136.

152. Zhu, Yuequan, Eric Allen Klomparens, Sichao Guo and Xiaokun Geng. "Neuroinflammation Caused by Mental Stress: The Effect of Chronic Restraint Stress and Acute Repeated Social Defeat Stress in Mice." *Neurol Res* 41 (2019): 762-769.

153. Weber, Michael D, Jonathan P Godbout and John F. Sheridan. "Repeated Social Defeat, Neuroinflammation, and Behavior: Monocytes Carry the Signal." *Neuropsychopharmacol* 42 (2017): 46-61.

154. Ramirez, Karol, Jaime Fornaguera-Trías and John F Sheridan. "Stress-Induced Microglia Activation and Monocyte Trafficking to the Brain Underlie the Development of Anxiety and Depression." *Curr Top Behav Neurosci* (2017): 155-172.

155. Welcome, Menizibeya O and Nikos E Mastorakis. "Stress-Induced Blood Brain Barrier Disruption: Molecular Mechanisms and Signaling Pathways." *Pharmacol Res* 157 (2020): 104769.

156. Fisher, Robert S, Barbara G Vickrey, Patricia Gibson and Bruce Hermann, et al. "The Impact of Epilepsy From the Patient's Perspective II: Views About Therapy and Health Care." *Epilepsy Res* 41 (2000): 53-62.

157. Frucht, Michael M, Mark Quigg, Carl Schwaner and Nathan B Fountain. "Distribution of Seizure Precipitants Among Epilepsy Syndromes." *Epilepsia* 41 (2000): 1534-1539.

158. Nakken, Karl O, Marit H Solaas, Marianne J Kjeldsen and Mogens L Friis, et al. "Which Seizure-Precipitating Factors Do Patients With Epilepsy Most Frequently Report?." *Epilepsy Behav* 6 (2005): 85-89.

159. Sperling, Michael R, Courtney A Schilling, David Glosser and Joseph I Tracy, et al. "Self-Perception of Seizure Precipitants and Their Relation to Anxiety Level, Depression, and Health Locus of Control in Epilepsy." *Seizure* 17 (2008): 302-307.

160. Klein, Pavel and Leonie van Passel. "Effect of Stress Related to the 9/11/2001 Terror Attack on Seizures in Patients With Epilepsy." *Neurology* 64 (2005): 1815-1816.

161. Neufeld, M Y, M Sadeh, D F Cohn and A D Korczyn. "Stress and Epilepsy: The Gulf War Experience." *Seizure* 3 (1994): 135-139.

162. Swinkels, W A M, M Engelsman, D G A Kasteleijn-Nolst Trenité and M G Baal, et al. "Influence of an Evacuation in February 1995 in the Netherlands on the Seizure Frequency in Patients With Epilepsy: A Controlled Study." *Epilepsia* 39 (1998): 1203-1207.

163. Rakhade, Sanjay N and Frances E Jensen. "Epileptogenesis in the Immature Brain: Emerging Mechanisms." *Nat Rev Neurol* 5 (2009): 380-391.

164. Tynan, Ross J, Sundresan Naicker, Madeleine Hinwood and Eugene Nalivaiko, et al. "Chronic Stress Alters the Density and Morphology of Microglia in a Subset of Stress-Responsive Brain Regions." *Brain Behav Immun* 24 (2010): 1058-1068.

165. Wohleb, Eric S, Mark L Hanke, Angela W Corona and Nicole D Powell, et al. "Beta-Adrenergic Receptor Antagonism Prevents Anxiety-Like Behavior, and Microglial Reactivity Induced by Repeated Social Defeat." *J Neurosci* 31 (2011): 6277-6288.

166. Wang, Ming and Yinghui Chen. "Inflammation: A Network in the Pathogenesis of Status Epilepticus." *Front Mol Neurosci* 11 (2018): 341.

167. Meng, Fanwei and Lifen Yao. "The Role of Inflammation in Epileptogenesis." *Acta Epileptol* 2 (2020): 1-19.

168. Benson, Melissa J, Silvia Manzanero and Karin Borges. "Complex Alterations in Microglial M1/M2 Markers During the Development of Epilepsy in Two Mouse Models." *Epilepsia* 56 (2015): 895-905.

169. Wu, Wenning, Yujiao Li, Yujia Wei and Dale B. Bosco, et al. "Microglial Depletion Aggravates the Severity of Acute and Chronic Seizures in Mice." *Brain Behav Immun* 89 (2020): 245-255.

170. Sá-Pereira, Inês, Dora Brites and Maria Alexandra Brito. "Neurovascular Unit: A Focus on Pericytes." *Mol Neurobiol* 45 (2012): 327-347.

171. Liebner, Stefan, Rick M Dijkhuizen, Yvonne Reiss and Karl H Plate, et al. "Functional Morphology of the Blood–Brain Barrier in Health and Disease." *Acta Neuropathol* 135 (2018): 311-336.

172. Varvel, Nicholas H, Jonas J Neher, Andrea Bosch and Wenyi Wang, et al. "Infiltrating Monocytes Promote Brain Inflammation and Exacerbate Neuronal Damage After Status Epilepticus." *Proc Natl Acad Sci* 113 (2016): E5665-E5674.

173. Özdemir, Hasan H, Esref Akil, Abdullah Acar and Yusuf Tamam, et al. "Changes in Serum Albumin Levels and Neutrophil-Lymphocyte Ratio in Patients With Convulsive Status Epilepticus." *Int J Neurosci* 127 (2017): 417-420.

174. Cheng, Shiqiang, Bei Han, Miao Ding and Yan Wen, et al. "Identifying Psychiatric Disorder-Associated Gut Microbiota Using Microbiota-Related Gene Set Enrichment Analysis." *Brief Bioinformatics* 21 (2020): 1016-1022.

175. Yang, Zhongli, Jingjing Li, Xiaohua Gui and Xiaoqiang Shi, et al. "Updated Review of Research on the Gut Microbiota and Their Relation to Depression in Animals and Human Beings." *Mol Psychiatry* 25 (2020): 2759-2772.

176. Xu, Hao-Ming, Hong-Li Huang, You-Lian Zhou and Hai-Lan Zhao, et al. "Fecal Microbiota Transplantation: A New Therapeutic Attempt From the Gut to the Brain." *Gastroenterol Res Pract* 2021 (2021): 6699268.

177. Zheng, Peng, Benhua Zeng, Meiling Liu, Jianjun Chen, Junxi Pan, Yu Han, Yiyun Liu et al. "The gut microbiome from patients with schizophrenia modulates the glutamate-glutamine-GABA cycle and schizophrenia-relevant behaviors in mice." *Science advances* 5 (2019):eaau8317.

178. Pan, Yuchen, Zhiyao Yu, Yuan Yuan, Jiapeng Han, Zhuo Wang, Hui Chen, Songyun Wang et al. "Alteration of autonomic nervous system is associated with severity and outcomes in patients with COVID-19." *Front physiol* 12 (2021): 630038.

179. Hernández Cáceres, J L, H Foyaca Sibat, R Hong, L Garcia, M Sautié, and V Namugowa. "Towards the estimation of the fractal dimension of heart rate variability data." *Electron J Biomed* 1(2004): 4-15.

180. Picchianti Diamanti, Andrea, Maria Manuela Rosado, Claudio Pioli and Giorgio Sesti, et al. "Cytokine release syndrome in COVID-19 patients, a new scenario for an old concern: the fragile balance between infections and autoimmunity." *Int J Mol Sci* 21 (2020): 3330.

181. Que, Yifan, Chao Hu, Kun Wan and Peng Hu, et al. "Cytokine release syndrome in COVID-19: a major mechanism of morbidity and mortality." *Int Rev Immunol* (2021): 1-14.

182. Lee, Daniel W, Rebecca Gardner, David L Porter and Chrystal U Louis, et al. "Current concepts in the diagnosis and management of cytokine release syndrome." *Am J Hematol* 124(2014): 188-195.

183. Zhang, Chi, Zhao Wu, Jia-Wen Li and Hong Zhao, et al. "Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality." *Int J Antimicrob Agents* 55(2020): 105954.

184. Toniati, Paola, Simone Piva, Marco Cattalini and Emirena Garrafa, et al. "Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia, Italy." *Autoimmun Rev* 19(2020): 102568.

185. Cantini, Fabrizio, Laura Niccoli, Daniela Matarrese and Emanuele Nicastri, et al. "Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact." *J Infect* 81(2020): 318.

186. Stebbing, Justin, Venkatesh Krishnan, Stephanie de Bono and Silvia Ottaviani, et al. "Mechanism of baricitinib supports artificial intelligence-predicted testing in COVID-19 patients." *EMBO Mol Med* 12(2020): e12697.

187. Richardson, Peter J, Mario Corbellino and Justin Stebbing. "Baricitinib for COVID-19: a suitable treatment?–Authors' reply." *Lancet Infect Dis* 20(2020): 1013-1014.

188. Rodriguez-Garcia, Jose Luis, Gines Sanchez-Nievas, Juan Arevalo-Serrano and Cristina Garcia-Gomez, et al. "Baricitinib improves respiratory function in patients treated with corticosteroids for SARS-CoV-2 pneumonia: an observational cohort study." *Rheumatology* 60(2021): 399-407.

189. Richardson, Peter, Ivan Griffin, Catherine Tucker and Dan Smith, et al. "Baricitinib as potential treatment for 2019-nCoV acute respiratory disease." *Lancet* 395(2020): e30–e31

190. Shakoory, Bita, Joseph A Carcillo, W Winn Chatham and Richard L Amdur, et al. "Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of the macrophage activation syndrome: Re-analysis of a prior Phase III trial." *Crit Care Med* 44(2016): 275.

191. Dinarello, Charles A, Anna Simon and Jos WM Van Der Meer."Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases." *Nat Rev Drug Discov* 11(2012): 633-652.

192. Pontali, Emanuele, Stefano Volpi, Giancarlo Antonucci and Marco Castellaneta, et al. "Safety and efficacy of early high-dose IV anakinra in severe COVID-19 lung disease." *J Allergy Clin Immunol* 146(2020): 213.

193. Dimopoulos, George, Quirijn de Mast, Nikolaos Markou and Maria Theodorakopoulou, et al. "Favorable anakinra responses in severe Covid-19 patients with secondary hemophagocytic lymphohistiocytosis." *Cell Host Microbe* 28(2020): 117-123.

194. Griffith, James Francis, Gregory Ernest Antonio and Shekhar Madhukar Kumta, et al. "Osteonecrosis of hip and knee in patients with severe acute respiratory syndrome treated with steroids." *Radiology* 235(2005): 168-175.

195. Grant, William B, Henry Lahore, Sharon L McDonnell and Carole A Baggerly, et al. "Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths." Nutrients 12(2020): 988.

196. Mariani, Erminia, Luca Cattini, Simona Neri and Marco Malavolta, et al. "Simultaneous evaluation of circulating chemokine and cytokine profiles in elderly subjects by multiplex technology: relationship with zinc status." *Biogerontology* 7(2006): 449-459.

197. Alexander, Jan, Alexey Tinkov, Tor A Strand and Urban Alehagen, et al. "Early nutritional interventions with zinc, selenium and vitamin D for raising anti-viral resistance against progressive COVID-19." *Nutrients* 12(2020): 2358.

198. Derwand, R, and M Scholz. "Does zinc supplementation enhance the clinical efficacy of chloroquine/hydroxychloroquine to win today's battle against COVID-19?" *Med Hypotheses* 142 (2020): 109815.

199. Zhang, Xiao-Jing, Juan-Juan Qin, Xu Cheng and Lijun Shen, et al. "In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19." *Cell Metab* 32(2020): 176-187.

200. Jawhara, Samir. "Could intravenous immunoglobulin collected from recovered coronavirus patients protect against COVID-19 and strengthen the immune system of new patients?" *Int J Mol Sci* 21(2020): 2272.

201. Delly, Fadi, Maryam J Syed, Robert P Lisak and Deepti Zutshi. "Myasthenic crisis in COVID-19." J Neurol Sci 414 (2020): 116888.

202. Xie, Yun, Song Cao, Hui Dong and Qingyun Li, et al. "Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19." *J Infect* 81(2020): 318.

203. Prete, Marcella, Elvira Favoino, Giacomo Catacchio and Vito Racanelli, et al. "SARS-CoV-2 infection complicated by inflammatory syndrome. Could high-dose human immunoglobulin for intravenous use (IVIG) be beneficial?." *Autoimmun Rev* 19(2020): 102559.

204. Cao, Wei, Xiaosheng Liu, Tao Bai and Hongwei Fan, et al. "High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019." *Open Forum Infect Dis* 7: 102.

205. Aljaberi, Rana, and Kholoud Wishah. "Positive outcome in a patient with coronavirus disease 2019 and common variable immunodeficiency after intravenous immunoglobulin." *Ann Allergy Asthma Immunol* 125(2020): 349-350.

206. Chen, Qian, Chaoying Hu, Ye Liu and Yun Liu, et al. "Safety and tolerability of high-dose ulinastatin after 2-hour intravenous infusion in adult healthy Chinese volunteers: a randomized, double-blind, placebo-controlled, ascending-dose study." *PloS one* 12(2017): e0177425.

207. Li, Dejun, Hongsheng Ji, Bao Zhao and Chunyang Xu, et al. "Therapeutic effect of ulinastatin on pulmonary fibrosis *via* downregulation of TGF-β1, TNF-α and NF-κB." *Mol Med Rep* 17(2018): 1717-1723.

How to cite this article: Sibat, Humberto Foyaca. "Neurocysticercosis, Epilepsy, COVID-19 and a Novel Hypothesis: Cases Series and Systematic Review." *Clin Schizophr Relat Psychoses* 15S (2021). Doi: 10.3371/CSRP.FH.121421