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Possible post-COVID epilepsy: A review of epilepsy monitoring unit admissions during the two years of COVID-19 pandemic

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ABSTRACT

Large scale healthcare data shows that new-onset epilepsy is noted in 0.3 % patients within 6 months of COVID-19 infection. We analyzed diagnostic epilepsy monitoring unit (EMU) evaluations to identify and report such cases. We thoroughly reviewed our EMU database and identified patients having "COVID" or "Corona" virus mention in their medical record from 03/15/2020 to 02/28/2022. Patients with epilepsy prior to COVID infection were excluded. Among 62 patients without prior epilepsy evaluated in the EMU for new-onset spells after confirmed COVID-19 infection, three patients were diagnosed with focal epilepsy. These three women without epilepsy risk factors had seizure onset at the time of, or within one to three months of, COVID-19 diagnosis. Their 3 T MRI imaging was non-lesional but revealed bilateral enlarged perivascular spaces. The video EEG monitoring was consistent with temporal or fronto-temporal lobe epilepsy in all three patients. Two of them developed drug-resistant epilepsy within six months of seizure onset. Our thorough analysis of diagnostic EMU evaluations during the two years of pandemic reveals three cases of post-COVID-19 epilepsy after non-symptomatic to mild disease. Although coincidental epilepsy onset cannot be ruled out, larger multicenter or national database investigations are needed to further analyze the possibility of post-COVID epilepsy.

Introduction

Almost a quarter of coronavirus disease (COVID-19) patients develop post-acute sequelae of SARS-CoV-2 infection (PASC), which prominently includes fatigue, anosmia/parosmia, concentration and memory impairment, headache, and insomnia among other symptoms [1,2]. The whole spectrum of neurological sequelae of COVID-19 is likely to emerge in the coming years. Many questions about the underlying pathophysiology remain unanswered. The landmark UK Biobank study comparing the pre- and post-COVID-19 MRI showed that even mild COVID-19 infection in non-hospitalized patients leads to significant changes in brain structure, specifically reduced gray matter thickness in the parahippocampal gyrus, orbitofrontal and anterior cingulate cortex [3]. These limbic and paralimbic structures play a critical role in focal epilepsy. However, epilepsy is not yet recognized as a sequela of COVID-19 [4]. Acute COVID-19 infection is associated with epileptiform abnormalities and seizures on continuous electroencephalogram (EEG) monitoring [5–7]. COVID-19 damages brain endothelial cells, and through the infiltration of immune cells, upregulates inflammatory cytokines and chemokines leading to inflammation [8]. Such changes can cause acute cortical irritation and epileptogenicity. Viral infections are known to cause neuronal excitation and epilepsy development through glial activation, blood–brain barrier breakdown, immune cell infiltration, and neuroinflammation [9].

An analysis of electronic health records (EHR) of 81 million people in the US recently found that COVID19 patients had a 0.81 % incidence of seizures and 0.3 % incidence of epilepsy within 6 months of COVID diagnosis, which has hazard ratio 1.6 to 1.9 times higher than well-matched influenza population [10]. Given the structural and neuroinflammatory changes from COVID, and large datasets revealing post-COVID epilepsy, we investigated epilepsy development as a sequela of COVID-19 infection in patients undergoing epilepsy monitoring unit (EMU) admission, and report three cases of new-onset focal epilepsy confirmed on video EEG monitoring that developed after COVID-19 infection.

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Methods

We queried the prospectively maintained EMU database of our level-4 comprehensive epilepsy center from 03/15/2020 to 02/28/2022. The electronically searchable database was used to screen the clinical history to identify patients with the mention of "COVID" or "Corona" virus. The EMU database of the patients identified by above process was thoroughly reviewed, particularly for the video EEG findings and ensuring that the seizure onset was any time after the COVID-19 diagnosis. Patients with epilepsy prior to COVID infection were excluded. Only the patients with seizure onset after COVID-19 who had confirmed epilepsy on EMU monitoring are reported here. Their relevant electro-clinical and diagnostic information was extracted. The brain MRIs and raw EEGs of the selected patientswere re-reviewed.

Results

As noted in the study patient flowchart (Fig. 1), the free-word search identified 109 patients with mention of "COVID" or "Corona" in their clinical history. They accounted for 5.4 % of the total patient population monitored in the EMU during the study period. Among these 109 patients, 47 had epilepsy history. Among the remaining 62 who underwent diagnostic EMU evaluation for new-onset spells after a reverse transcription polymerase chain reaction test of nasopharyngeal swab confirmed COVID-19 infection, three (4.8 %) patients were diagnosed with new-onset focal epilepsy. Rest of the patients did not have any epileptiform discharge or epileptic seizure captured during the EMU monitoring to confirm epilepsy.

Patient 1

A 32-year-old right-handed female with diabetes mellitus type II (DMII), obesity, obstructive sleep apnea, depression, and alcoholism was brought to the emergency department (ED) after a first-time seizure described as whole-body convulsion. The patient was at baseline by the time of ED arrival. She had mild creatine kinase and white blood cell count elevation, and urine was positive for marijuana. Her last alcoholic drink was the previous day. She tested positive for COVID but was asymptomatic and denied sick contacts. She had no history of febrile seizures, developmental delays, head trauma, strokes, CNS infection, or family history of seizures (hereafter referred as epilepsy risk factors). This was her first lifetime seizure. Her antibody prevalence in epilepsy and encephalopathy (APE2) score [11] was 0 out of 13 (excluding 2 points for CSF findings), making autoimmune etiology unlikely. anti-seizure medication (ASM) was not started despite EEG showing right temporal sharp waves due to the possibility of acute symptomatic seizure from alcohol withdrawal in the setting of non-symptomatic COVID-19. This was her first lifetime EEG. A 3-tesla (3 T) MRI was non-lesional. She stopped alcohol use after the first seizure. Almost a month later, she presented to the ED due to another similar seizure. She was started on levetiracetam, and later switched to oxcarbazepine because of mood–related adverse effects. Soon zonisamide was added and despite the use of two ASMs at appropriate doses, seizures with impaired awareness continued. She was admitted to our EMU for diagnosis confirmation and potential pre-surgical evaluation. Her interictal findings showed exclusively right fronto-temporal (maximum F8/T8) sharp waves. We captured seizures that started with an aura of feeling hot and increased heart rate followed by impaired awareness, and oro-manual automatisms. Ictal EEG showed a characteristic high amplitude theta activity arising from the right frontotemporal region (Fig. 2A) in all seizures. Magnetoencephalography showed two tight dipole clusters in the right temporal lobe (Fig. 2B). Positron emission tomography showed hypometabolism in the anterior aspect of the right superior temporal gyrus (Fig. 2C). At the last follow-up, 19 months since COVID-19 diagnosis, she is on oxcarbazepine and zonisamide, and despite escalating doses, she was still having frequent daily seizures including generalized-tonic clonic. Therefore, she is undergoing work-up for potential epilepsy surgery.

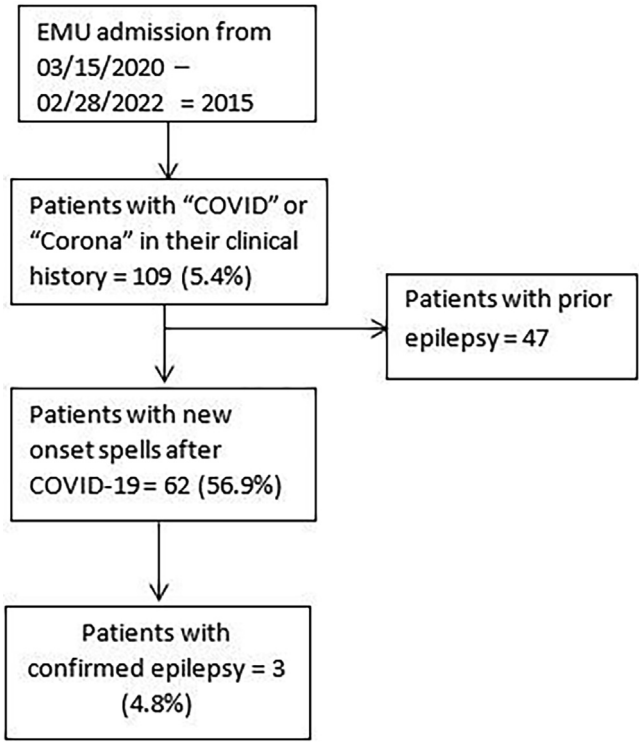

Fig. 1. Study Flowchart (Percentages shown as proportion of the number of patients a step-above in the flowchart).

Patient 2

A 36-year-old right-handed female with no comorbid medical history tested positive for COVID after 3 days of anosmia onset. Her COVID test remained positive 28-days later. Almost three months after COVID-19 diagnosis, she had an episode of "passing out while driving," leading to an accident. On presentation, her initial workup was unremarkable, including head CT, chest X-ray, urinalysis, CMP, CBC, and lactate. EEG showed epileptiform sharp waves over the right temporal (maximum T8 or P8) head region, and she was started on levetiracetam. She then had recurrent episodes of left ear ringing followed by right facial numbness and hypersalivation. Two months later, she started having episodes of repeating the phrase "mmm here we go", followed by impaired awareness for 10 s. These episodes continued despite compliance with levetiracetam and addition of oxcarbazepine for clinical suspicion of epilepsy. Her 3 T MRI was reported as normal, and her CSF was negative for inflammatory biomarkers like WBC count and autoimmune antibodies. She had no epilepsy risk factors.

The diagnostic EMU evaluation confirmed right temporal lobe epilepsy. Interictal EEG showed sharp waves over the right temporal (maximum T8 or P8) region. Three typical focal-onset aware seizures were recorded, characterized by vocal humming followed by mouth and bilateral hand automatisms with a left hand dystonic posturing. Ictal pattern showed right temporal rhythmic delta activity evolving to rhythmic theta rhythm (Fig. 3A). At the last follow-up, 11 months after COVID-19 diagnosis, she was continuing to have monthly seizures on oxcarbazepine, lamotrigine, and lacosamide.

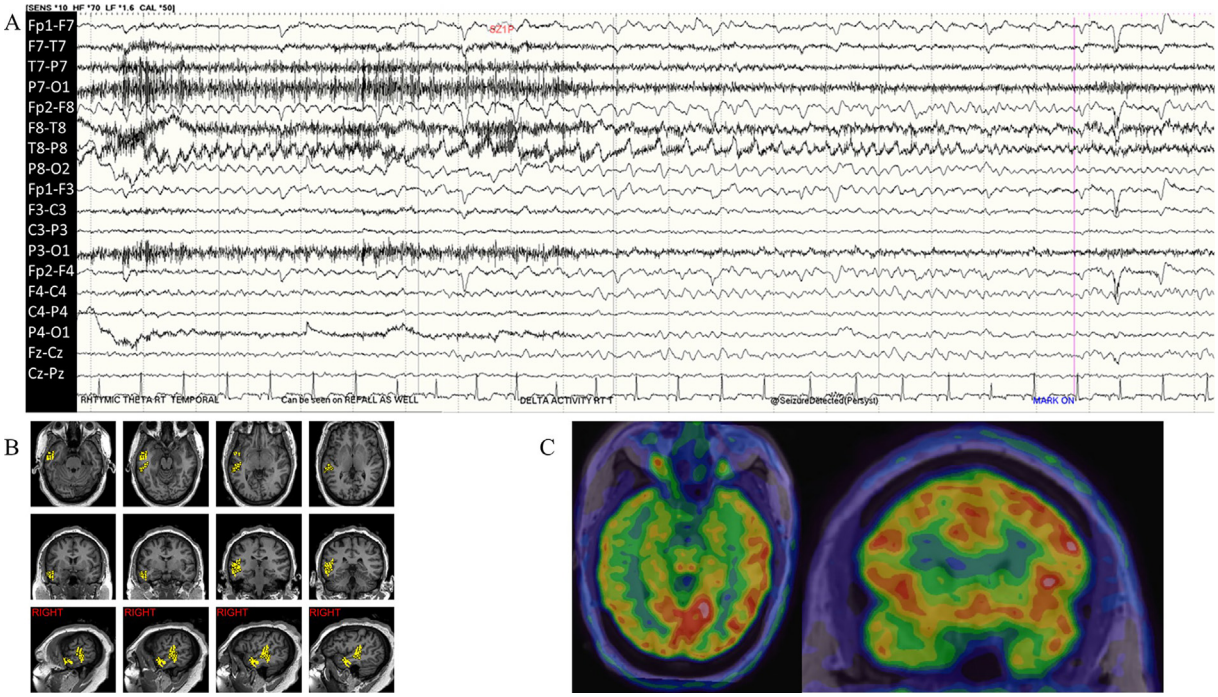

Fig. 2. EEG, magnetoencephalography, and positron emission tomography of Patient 1. A) Ictal EEG showing seizure activity arising from the right fronto-temporal region. Longitudinal bipolar montage. Sensitivity 10 μV, 21 s EEG page. B) Two tight dipole clusters in the right temporal lobe displayed on magnetoencephalography. C) Hypometabolism in the anterior aspect of the right superior temporal gyrus on positron emission tomography.

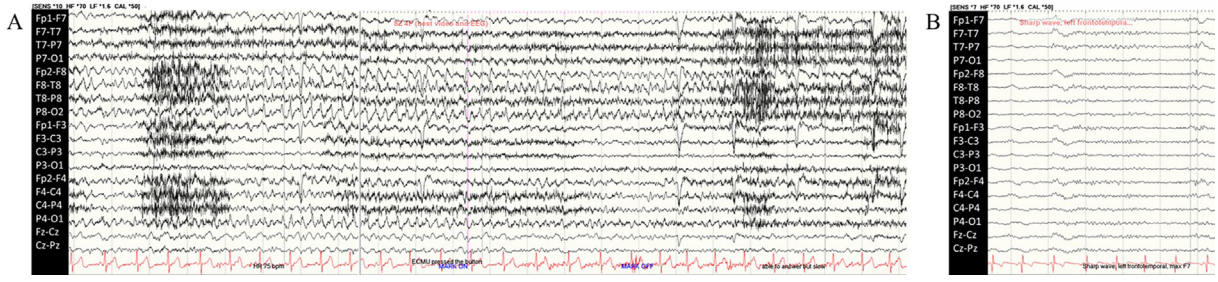

Fig. 3. EEG of Patient 2 and 3. A) Ictal EEG of Patient 2 showing seizures activity arising from the right fronto-temporal region. Longitudinal bipolar montage. Sensitivity 10 μV, 22 s EEG page. B) Interictal EEG of Patient 3 demonstrating anterior temporal sharp waves. Longitudinal bipolar montage. Sensitivity 7 μV, 6.5 s EEG page.

Patient 3

A 52-year-old right-handed female with history of hypertension and DMII developed fever and diarrhea, which resolved in 3 days. Then she had nausea, vomiting, and abdominal pain for 3 weeks. On presentation, she had an acute kidney injury (AKI), which resolved with hydration. She also tested positive for COVID-19. She was discharged home in stable health after 4 days. Soon after discharge, she started to become episodically confused and was re-admitted to the local hospital. She had readmissions to her local hospital over the next several weeks for similar complaints but the routine tests remained negative. Three months from her initial positive test, a three-day video-EEG showed left anterior temporal sharp waves, but no seizures. She was discharged on lamotrigine. Her 3 T MRI brain was non-lesional and only showed minimal white matter disease. CSF testing performed during the EMU admission was with in normal limits twice, including zero white cells, negative oligoclonal bands, negative infectious markers (meningitis/encephalitis panel, Lyme, and VDRL) and negative cytology. Serum and CSF autoimmune encephalitis and paraneoplastic antibody testing was also negative. She complained of short-term memory deficits and scored 27/30 on mini-mental state examination (MMSE, losing points on month, date, and day) during a clinic visit after hospital discharge. She self-discontinued lamotrigine and the caregiver reported increased confusional episodes and memory issues. Her paternal uncle had epilepsy, but she had no other epilepsy risk factors. She was admitted to our EMU for episode characterization, which were not captured during seven days of monitoring despite ASM discontinuation. However, frequent left temporal sharp waves (T7 > P7) were noted on EEG (Fig. 3B). She was diagnosed with likely non-lesional left temporal focal epilepsy, based on clinical history and interictal EEG findings, and was discharged on oxcarbazepine. At the last follow-up, 15 months after COVID-19 diagnosis, she was not having any further episodes of confusion on oxcarbazepine monotherapy.

MRI findings

The visual re-review did not reveal clear epileptogenic lesions. However, T2-weighted images showed extensive, bilateral enlarged perivascular spaces in all three patients (Fig. 4). Patients did not have MRIs prior to above reported presentation to allow for pre- and post-COVID comparison.

Discussion

Our review of EMU admissions during the two years of COVID-19 pandemic reveals three adults lacking epilepsy risk-factors or

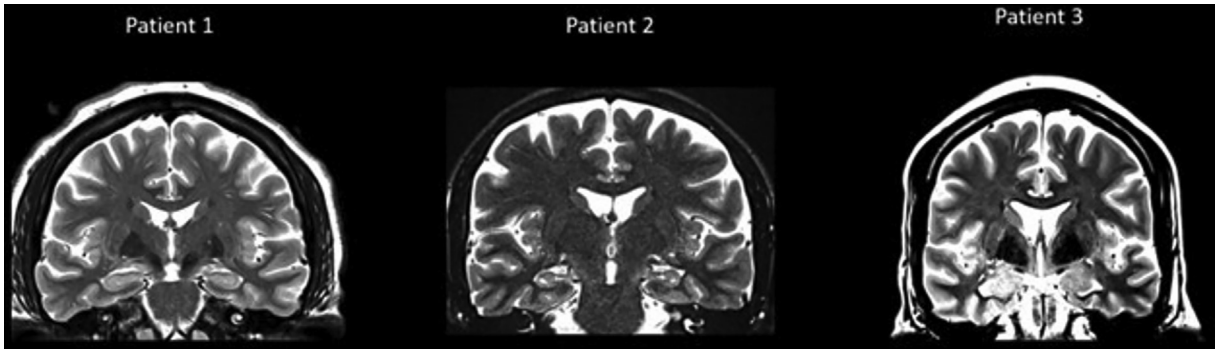

Fig. 4. T2-weighted coronal images showing enlarged perivascular spaces. MRIs of all three patients were reported as normal.

other identifiable etiologies who developed new-onset focal epilepsy following SARS-CoV-2 infection, suggesting that epilepsy could be a possible sequela of COVID-19. The three patients had asymptomatic (Patient 1) to mild (Patient 2 and 3) COVID-19, not requiring hospitalization or COVID-specific treatment (Patient 3 later admitted due to AKI). While Patient 1 was COVID-19 positive but asymptomatic at the time of her first seizure, the other two developed seizures within 1 – 3 months of COVID-19. Our findings are consistent with the emerging literature showing that the risk of epilepsy development is higher in patients who did not require hospitalization for COVID-19, and the median time to seizure onset in this patient population is 41 days. However, it is relevant to note that epilepsy development in the absence of identifiable risk-factors is not uncommon.

Several mechanisms for seizures in the acute COVID-19 settings are proposed [5,12]. A case-series of 50 PASC patients report one person with seizures after COVID-19 related hospitalization [13]. Another patient developed temporal-lobe epilepsy, confirmed by EMU evaluation, approximately-six-weeks after COVID-19 infection requiring hospitalization [14]. These rare cases seem to be consistent with 0.3% incidence of epilepsy within 6 months of COVID diagnosis [10]. The absolute risk of post-COVID epilepsy is low and could only have been detected through large-scale EHR datasets [10]. However, such datasets lack the patient level details that are required to understand the phenotype of rare disease. Additionally, they do not have validated diagnosis, which is especially concerning for condition like seizures and epilepsy given its several clinical mimickers. It is best highlighted by only 5% of patients with new-onset spells after COVID diagnoses with confirmed epilepsy in 2-years of EMU monitoring during the pandemic. Our study is not designed to provide estimates of incidence or prevalence of post-COVID epilepsy.

Our three cases, and the one reported in the literature [14], have temporal or fronto-temporal epilepsy. Although a common region for focal epilepsy, this localization is highly relevant in the context of structural changes in the limbic and paralimbic cortex noted on the MRIs after mild COVID-19 compared to pre-COVID imaging [3]. Due to the small sample size, we did not perform advanced MRI post-processing. Our visual re-review of MRIs revealed a shared neuroimaging feature among the three patients – extensive, bilaterally enlarged perivascular spaces. Recent studies reveal enlarged perivascular spaces in epilepsy patients [15], and their potential to serve as imaging biomarkers of post-stroke epilepsy development [16]. However, an etio-pathogenic association of this perivascular space enlargement to the temporal or fronto-temporal epilepsy in our patients is unclear. Given their bilateral presence, these are more likely consistent with the perivascular space enlargement noted on the post-mortem pathology and in-vivo MRI imaging of COVID-19 patients, which is proposed as a marker of neuroinflammation [17,18]. Our patients did not have clinical, serological, or CSF (Patient 2 and 3) signs of neuroinflammation and hence, did not receive immunomodulatory therapies.

Critically ill COVID-19 patients show neuropathological changes in form of mild astrogliosis and microglial activation [19,20]. A pathogenic association of these changes with epileptogenesis is speculative, but not improbable. Another, more plausible explanation is that the COVID-19 infection could be a sufficient 'second-hit' for epileptogenesis in these three patients who otherwise lacked the typical epilepsy risk factors. Additionally, the rapid drug-resistance development in a matter of months in Patients 1 and 2 is noteworthy [21]. A major limitation of our study is the sample size. However, that may be indicative of the rarity of such events. Additionally, the three patients show differences in epilepsy onset in relation to COVID-19 positivity, and Patient 1 lacks CSF testing. Our reporting on these three patients with post-COVID epilepsy behooves future multi-center or national database analysis to further explore an association between COVID-19 and epileptogenesis in some patients.

Conclusion

While a large EHR dataset study clearly shows increased risk of epilepsy development after COVID-19 compared to influenza, overall, such cases are infrequent. In our single-center, first of its kind analysis of EMU diagnostic evaluations during the two years of pandemic, possible post-COVID-19 epilepsy was noted among 5 % of individuals with new-onset spells after COVID-19. A coincidental new-onset epilepsy unrelated to non-symptomatic to mild COVID-19 disease cannot be ruled out. However, as the scope of COVID-19′s complications and long-term outcomes continue to evolve, it is critical to report on rare but possible disease states that emerge in the setting of COVID-19.

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Ethical statement

This research was ethically performed and approved by the Institutional Review Board (IRB) of the Cleveland Clinic.

Declaration of Competing Interest

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

References

[1] Bull-Otterson L, Baca S, Saydah S, Boehmer TK, Adjei S, Gray S, et al. Post–COVID Conditions Among Adult COVID-19 Survivors Aged 18–64 and ≥65

Years — United States, March 2020–November 2021. MMWR Morb Mortal Wkly Rep 2022;71(21):713–7.
[2] Sneller MC, Marques AR, Liang CJ, Chung JY. A Longitudinal Study of COVID-19 Sequelae and Immunity. Ann Intern Med 2022;175(12):W153.
[3] Douaud G, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, McCarthy P, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature. 2022 Apr;604(7907):697-707. doi: 10.1038/s41586-022-04569-5. Epub 2022 Mar 7. PMID: 35255491; PMCID: PMC9046077.
[4] Nolen LT, Mukerji SS, Mejia NI. Post-acute neurological consequences of COVID-19: an unequal burden. Nat Med 2022 Jan;28(1):20–3. https://doi.org/10.1038/s41591-021-01647-5. PMID: 35039657.
[5] Hepburn M, Mullaguri N, George P, Hantus S, Punia V, Bhimraj A, et al. Acute Symptomatic Seizures in Critically Ill Patients with COVID-19: Is There an Association? Neurocrit Care 2021;34(1):139–43.
[6] Lin L, Al-Faraj A, Ayub N, Bravo P, Das S, Ferlini L, et al. Electroencephalographic Abnormalities are Common in COVID-19 and are Associated with Outcomes. Ann Neurol. 2021 May;89(5):872-883. doi: 10.1002/ana.26060. Epub 2021 Mar 24. PMID: 33704826; PMCID: PMC8104061.
[7] Louis S, Dhawan A, Newey C, Nair D, Jehi L, Hantus S, et al. Continuous electroencephalography characteristics and acute symptomatic seizures in COVID-19 patients. Clin Neurophysiol 2020;131(11):2651–6.
[8] Johansson A, Mohamed MS, Moulin TC, Schiöth HB. Neurological manifestations of COVID-19: A comprehensive literature review and discussion of mechanisms. J Neuroimmunol 2021;358:577658.
[9] DePaula-Silva AB, Bell LA, Wallis GJ, Wilcox KS. Inflammation Unleashed in Viral-Induced Epileptogenesis. EpilepsyCurr 2021 Sep 27;21(6):433–40. https://doi.org/10.1177/15357597211040939. PMID: 34924851; PMCID: PMC8652320.
[10] M. Taquet O. Devinsky J.H. Cross P.J. Harrison A. Sen Incidence of Epilepsy and Seizures Over the First 6 Months After a COVID-19 Diagnosis: A Retrospective Cohort Study 10.1212/WNL.0000000000201595.
[11] Dubey D, Pittock SJ, McKeon A. Antibody Prevalence in Epilepsy and Encephalopathy score: Increased specificity and applicability. Epilepsia 2019 Feb;60(2):367–9. https://doi.org/10.1111/epi.14649. PMID: 30727035.
[12] Nikbakht F, Mohammadkhanizadeh A, Mohammadi E. How does the COVID-19 cause seizure and epilepsy in patients? The potential mechanisms. Mult Scler Relat Disord 2020;46:102535.
[13] Bungenberg J, Humkamp K, Hohenfeld C, Rust MI, Ermis U, Dreher M, et al. Long COVID-19: Objectifying most self-reported neurological symptoms. Ann Clin Transl Neurol 2022;9(2):141–54.
[14] Park S, Majoka H, Sheikh A, Ali I. A presumed case of new-onset focal seizures as a delayed complication of COVID-19 infection. Epilepsy & Behavior Reports 2021;16:100447.
[15] Feldman RE, Rutland JW, Fields MC, Marcuse LV, Pawha PS, Delman BN, et al. Quantification of perivascular spaces at 7 T: A potential MRI biomarker for epilepsy. Seizure 2018;54:11–8.
[16] Yu N, Sinclair B, Posada LMG, Chen Z, Di Q, Lin X, et al. Asymmetric distribution of enlarged perivascular spaces in centrum semiovale may be associated with epilepsy after acute ischemic stroke. CNS Neurosci Ther 2022;28(3):343–53.
[17] Kantonen J, Mahzabin S, Mäyränpää MI, Tynninen O, Paetau A, Andersson N, et al. Neuropathologic features of four autopsied COVID-19 patients. BrainPathol 2020;30(6):1012–6.
[18] Langan MT, Smith DA, Verma G, Khegai O, Saju S, Rashid S, et al. Semi-automated Segmentation and Quantification of Perivascular Spaces at 7 Tesla in COVID-19. Front Neurol 2022 Apr;13:. https://doi.org/10.3389/fneur.2022.846957. PMID: 35432151; PMCID: PMC9010775846957.
[19] Matschke J, Lütgehetmann M, Hagel C, Sperhake JP, Schröder AS, Edler C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. The Lancet Neurology 2020;19(11):919–29.
[20] Thakur KT, Miller EH, Glendinning MD, Al-Dalahmah O, Banu MA, Boehme AK, et al. COVID-19 neuropathology at Columbia University Irving Medical Center/New York Presbyterian Hospital. Brain 2021;144(9):2696–708.
[21] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010 Jun;51(6):1069-77. doi: 10.1111/j.1528-1167.2009.02397.x. Epub 2009 Nov 3. Erratum in: Epilepsia. 2010 Sep;51(9):1922. PMID: 19889013.