INCIDENCE OF ACUTE SYMPTOMATIC SEIZURES IN PATIENTS WITH COVID-19: A SINGLE-CENTER STUDY

Ivana Šušak Sporiš1,2,3,4, Davor Sporiš1,2,3,4, Zrinka Čolak Romić1, Petra Bago Rožanković1,5 and Silvio Bašić1

1Department of Neurology, Dubrava University Hospital, Zagreb, Croatia; 2Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia; 3Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia; 4University of Applied Health Science in Zagreb, Zagreb, Croatia; 5Chatolic University of Croatia, Zagreb, Croatia

SUMMARY – The most common neurological symptoms in patients with SARS-CoV-2 infection are headache, myalgia, encephalopathy, dizziness, dysgeusia and anosmia, making more than 90 percent of neurological manifestations of COVID-19. Other neurological manifestations such as stroke, movement disorder symptoms or epileptic seizures are rare but rather devastating, with possible lethal outcome. The primary aim of this study was to estimate the prevalence of acute symptomatic seizures among COVID-19 patients, while secondary aim was to determine their possible etiology. Out of 5382 patients with COVID-19 admitted to Dubrava University Hospital from November 1, 2020 until June 1, 2021, 38 (seizure rate 0.7%) of them had acute symptomatic seizures. Of these 38 patients, 29 (76.3%) had new-onset epileptic seizures and nine (23.7%) patients with previous epilepsy history had breakthrough seizures during COVID-19. Although acute symptomatic seizures are an infrequent complication of COVID-19, seizure risk must be considered in these patients, particularly in the group of patients with a severe course of the disease. Accumulation of proinflammatory cytokines may contribute to the occurrence of seizures in patients with COVID-19, but seizures may also be secondary to primary brain pathology related to COVID-19, such as stroke or encephalitis.

Key words: Seizures; Epilepsy; COVID-19; SARS-CoV-2

Introduction

Since the beginning of the outbreak in December 2019, the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has caused more than 195 million confirmed infections and more than 4 million deaths1. Like other coronaviruses, SARS-CoV-2 is primarily a respiratory virus, mostly causing general and respiratory symptoms such as fever, cough, dyspnea, fatigue, but what makes it specific is its ability to affect other organs including central and peripheral nervous system2,3. The most common neurological symptoms are headache, myalgia, encephalopathy, dizziness, dysgeusia and anosmia, making more than 90 percent of neurological manifestations of COVID-19, both at the beginning or during the course of the disease1. Other neurological manifestations such as stroke, movement disorder symptoms or epileptic seizures are rare but rather devastating, with possible lethal outcome3. The prevalence of epileptic seizures in COVID-19 patients has been studied before, but reports on the incidence of acute symptomatic seizures vary3,6.

The primary aim of this study was to estimate the prevalence of acute symptomatic seizures among COVID-19 patients, while secondary aim was to determine their possible etiology.
Patients and Methods

This observational, retrospective study recruited all patients admitted to Dubrava University Hospital during the period from November 1, 2020 until June 1, 2021. Since the beginning of the COVID-19 pandemic, Dubrava University Hospital had been converted into a regional COVID hospital. All patients admitted to the Hospital were aged 18 years and older, were positive for nasal swab SARS-CoV-2 RNA quantitative polymerase chain reaction (PCR) test, and had moderate to critical form of the disease. Out of the total number of patients hospitalized during this period, we analyzed the number of patients who had acute symptomatic seizures at the time of COVID-19 symptom onset or during COVID-19. Acute symptomatic seizures, defined as clinical seizures occurring at the time of a systemic insult or in close temporal relationship with a documented brain insult, included new-onset seizures in patients without prior history of epilepsy and breakthrough seizures in patients with prior history of well-controlled epilepsy. Patients with a history of epilepsy and seizures in the last two years were not included in the study. Diagnosis of epileptic seizure was established by neurologists. Seizures were classified according to the International League Against Epilepsy operational classification of seizure types. Demographic characteristics, as well as medical records that included medical history, radiological and laboratory findings, and treatment course data were taken from the Hospital electronic system. All patients had laboratory findings that included blood gases, complete blood count, C-reactive protein, renal and liver functions, electrolytes, and coagulation profile. Each patient underwent chest x-ray or chest computed tomography (CT), and CT or magnetic resonance imaging of the brain. In addition, all patients underwent electroencephalography (EEG) primarily to confirm or exclude status epilepticus, while cerebrospinal fluid (CSF) analysis was performed in cases where it was indicated.

The severity of COVID-19 was determined according to the World Health Organization guidelines as follows: (1) mild disease: symptomatic patients without evidence of viral pneumonia or hypoxia; (2) moderate disease: patients with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia; (3) severe disease: clinical signs of pulmonary (fever, cough, dyspnea, fast breathing) plus one of the following: respiratory rate >30 breaths/min, severe respiratory distress or \( \text{SpO}_2 < 90\% \) on room air; and (4) critical disease: patients with acute respiratory distress syndrome, sepsis or septic shock.

The study was approved by the Ethics Committee of Dubrava University Hospital. Data were expressed as number and percent or means ± standard deviation (SD).

Results

From November 1, 2020 until June 1, 2021, 5382 patients with confirmed SARS-CoV-2 infection were hospitalized at Dubrava University Hospital. During that period, 38 patients met the inclusion criteria, having new-onset seizures in cases without prior history of epilepsy or breakthrough seizures in cases with prior history of epilepsy. Demographic and clinical data of study patients are shown in Table 1. Out of 38 patients (seizure rate 0.7%), 29 (76.3%) had new-onset epileptic seizures and nine (23.7%) with previous epilepsy history had breakthrough seizures during COVID-19 (Table 2).

In the group of new-onset epileptic seizures without prior epilepsy history, the possible etiologic factor for seizures was not confirmed by laboratory or neuroimaging studies in five patients, while metabolic imbalance (one or more metabolic disorders) and/or severe hypoxemia was detected in 14 patients. In ten patients, primary brain pathology was confirmed with neuroimaging studies, some accompanied by metabolic and/or hypoxic derangements. Two of ten patients with primary brain pathology had acute stroke, 2 had lymphocytic pleocytosis without confirmed SARS-CoV-2 in CSF, one patient was diagnosed with posterior reversible encephalopathy syndrome (PRES) after complete workout, and one patient had a diagnosis of COVID-19 encephalopathy. In addition, in the group of patients with new-onset seizures and primary brain pathology, two patients had a stroke history and brain metastases each. Both patients with stroke history had a severe form of COVID-19 with severe hypoxemia and/or metabolic disturbances, while one of the two patients with brain metastases had significant metabolic imbalance and hypoxemia. The other patient with brain metastases had elevated lymphocytes, without significant deviations in other laboratory findings.
Out of the nine patients with breakthrough seizures and a history of epilepsy, metabolic cause and/or hypoxemia was confirmed in six patients. Of the remaining three patients, one patient had a history of traumatic brain injury and well-controlled post-traumatic epilepsy, while another one had a history of stroke and well-controlled post-stroke epilepsy. Both patients were without significant deviations in laboratory findings except for elevated inflammatory markers and fever. In this group, one patient had normal neuroimaging finding and no other cause of breakthrough seizures was confirmed.

Nine (23.7%) of 38 patients included in the study met the criteria for the diagnosis of epileptic status, six of them without pre-existing epilepsy.

### Discussion

Although SARS-CoV-2 is considered primarily a respiratory virus, patients with COVID-19 may experience a wide range of clinical manifestations including neurological symptoms. The angiotensin-converting enzyme 2 (ACE2) receptor provides SARS-CoV-2 entry route to human host cell with proven neurotropic potential of this virus\(^\text{10}\). According to different studies, neurological symptoms occur in 36.4%-82.3% of patients with COVID-19\(^\text{3,10,11}\). The severity of neuro-

### Table 1. Demographic and clinical characteristics of patients with COVID-19 and acute symptomatic seizures

| Patient characteristic | Total number of patients with seizures N=38 |
|------------------------|---------------------------------------------|
| Age (years), mean (SD) | 61.65 (18.29%) |
| Male, n (%)            | 21 (55.3%) |
| Female, n (%)          | 17 (44.7%) |
| Time elapsed between COVID-19 onset and seizure (days), mean (SD) | 7.69 (4.24) |
| Seizure type:          |                             |
| • focal, n (%)         | 18 (47.4%) |
| • generalized, n (%)   | 20 (52.6%) |
| Status epilepticus, n (%): |                               |
| • without history of epilepsy, n | 6   |
| • with history of epilepsy, n | 3   |

### Table 2. Seizure risk factors in patients with COVID-19 and acute symptomatic seizures

| Total number of patients N=38 | Patients with new-onset seizures n=29 | Patients with breakthrough seizures and history of epilepsy n=9 |
|-------------------------------|--------------------------------------|-------------------------------------------------------------|
| Undefined underlying etiology | 8 | 5 | 3 |
| Metabolic derangement:        |                             |                             |                             |
| hyperglycemia (>25.0 mmol/L)  | 16 | 12 | 4 |
| hypoglycemia (<2.2 mmol/L)   | 2 | 1 | 1 |
| hyponatremia (<115 mmol/L)   | 2 | 2 | 2 |
| hypocalcemia (<1.2 mmol/L)   | 5 | 3 | 2 |
| hypomagnesemia (<0.3 mmol/L) | 3 | 2 | 3 |
| urea nitrogen (>30 mmol/L)   | 1 | 1 | 0 |
| creatinine (>700 mmol/L)     | 4 | 3 | 1 |
| Hypoxia                       | 3 | 2 | 1 |
| Primary brain pathology:      |                             |                             |                             |
| acute ischemic stroke         | 2 | 2 | 0 |
| lymphocytic pleocytosis       | 2 | 2 | 0 |
| PRES                          | 1 | 1 | 0 |
| encephalopathy                | 1 | 1 | 0 |
| previous ischemic stroke      | 3 | 2 | 1 |
| brain metastases              | 2 | 2 | 0 |
| traumatic brain injury        | 1 | 0 | 1 |
| Sepsis                        | 1 | 1 | 0 |

PRES = posterior reversible encephalopathy syndrome
Patients with COVID-19 are more prone to coagulation disorders such as elevated D-dimers or diffuse intravascular coagulation. Persistent inflammation, as well as the effect of cytokines such as IL-6 could be an important activator of the coagulation cascade. Additionally, endothelial artery damage caused by direct virus cell entry can aggravate coagulation activation. Stroke was demonstrated to be a rare but potentially life-threatening complication of COVID-19, affecting approximately 1%-3% of hospitalized patients, and up to 6% of those in the intensive care unit. In the present study, two patients had acute symptomatic seizures following acute stroke. Acute ischemia leads to elevation of extracellular glutamate, hypoperfusion, impaired ion channel function, as well as BBB disruption. High levels of glutamate can activate AMPA and NMDA receptors leading to neuronal apoptosis or death. In addition to the two patients with acute stroke, another two patients with a history of previous stroke experienced new-onset seizures during COVID-19. Although stroke can cause late seizures by the mechanisms that include gliosis, chronic inflammation, apoptosis or loss of plasticity, and in hemorrhagic stroke, hemosiderin deposits can lead to neuronal hyperexcitability, both of our patients had severe metabolic derangements and one of them had severe hypoxemia. In two patients with newly diagnosed metastatic brain tumors, one of them with a severe course of COVID-19, new-onset seizures were established. Generally, seizures more commonly represent clinical manifestation of glial tumors than brain metastases. About 35% of patients with metastatic brain tumors have seizures and seizures are the initial symptom in only 20% cases. The occurrence of new-onset seizures in both patients with newly diagnosed brain metastases may have been unrelated to COVID-19 infection, but one patient had significant metabolic imbalance and hypoxemia, while the other one had prolonged fever and mild hypoxemia, which in our opinion could have contributed to the occurrence of seizures. In all of these patients, including those with primary brain pathology, it is rather challenging to establish clear etiologic factor in the clinical setting of COVID-19, taking into consideration all the systemic effects of the disease and medications administered.

Encephalitis and encephalopathy are among the major and devastating SARS-CoV-2-associated CNS...
complications\textsuperscript{25}. The occurrence of seizures following encephalitis is well known. Although two of our patients with new-onset seizures had CSF lymphocytic pleocytosis, the diagnosis of COVID-related meningoencephalitis could not be made due to the lack of PCR evidence of SARS-CoV-2 in the CSF, which has also been documented in other studies\textsuperscript{26,27}. Neurological manifestations of COVID-19 could be mediated through the immune related mechanisms within CNS. Several studies demonstrated anti-SARS-CoV-2 antibodies within the CSF, including antibodies against S1 protein, S2 protein and nucleoprotein of SARS-CoV-2 in the CSF of patients who presented with encephalopathy\textsuperscript{28}. Encephalopathy is common in older patients, presenting with a variety of symptoms, yet it remains poorly characterized\textsuperscript{25,29}. In our study, one patient had new-onset seizure as one of the presenting symptoms of COVID-19 encephalopathy. Rare cases of COVID-19-associated PRES have been described as a COVID-19 complication; in the present study, one patient with the diagnosis of PRES developed new-onset seizures\textsuperscript{30,31}.

In the group of patients with breakthrough seizures and a history of controlled epilepsy, six of nine patients had significant metabolic impairment or/and hypoxemia. Such a high percentage of the potential metabolic/ischemic etiology of seizures in both groups of our patients (patients with and without prior history of epilepsy) could be explained by the specific patient population in our hospital, with around 70\% of them having severe form of COVID-19. Since patients with severe COVID-19 may experience hypoxia, as well as multiorgan failure and severe metabolic derangements, it is plausible to expect the occurrence of clinical or subclinical acute symptomatic seizures in some patients\textsuperscript{3,14}. Furthermore, fever can contribute to seizure exacerbation.

In our patient cohort, there were nine patients with established status epilepticus. All patients with status epilepticus had severe or critical form of COVID-19. Some subclinical seizures could be misdiagnosed as encephalopathy in patients with COVID-19, which makes EEG monitoring extremely important in high-risk patients with COVID-19 and encephalopathy. EEG findings in such patients can help identify pathologic patterns and enable a diagnosis of status epilepticus.

Exhaustive documentation on neurological symptoms, detailed clinical, electrophysiological and radiological investigations of patients, as well as laboratory studies including CSF analysis may clarify the etiology of seizures and other neurological manifestations, so that patients can be provided with appropriate treatment.

**Conclusion**

Patients with COVID-19 commonly have neurological manifestations but acute symptomatic seizures are an infrequent complication of this disease. Nevertheless, seizure risk must be considered in these patients, particularly in the group of patients with severe course of the disease. Accumulation of proinflammatory cytokines may contribute to the occurrence of seizures in patients with COVID-19 but seizures may also be secondary to primary brain pathology related to COVID-19, such as stroke or encephalitis. The literature on this issue continues to evolve and more research is needed to demonstrate the exact mechanism of seizures in patients with COVID-19.

**References**

1. World Health Organization [Internet]. WHO Coronavirus (COVID-19) Dashboard; c2021 [cited 2021 Jul 27]. Available from: https://covid19.who.int

2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5

3. Liotta EM, Batra A, Clark JR, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in COVID-19 patients. Ann Clin Transl Neurol. 2020;7(11):2221-30. doi: 10.1002/acn3.51210.

4. 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. doi: 10.1016/j.msard.2020.102535.

5. Lu L, Xiong W, Liu D, et al. New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: a retrospective multicenter study. Epilepsia. 2020;61(s):e49-e53. doi: 10.1111/epi.16524.

6. Khedr EM, Shoyb A, Mohammaden M, Saber M. Acute symptomatic seizures and COVID-19: hospital-based study. Epilepsy Res. 2021;174:106650. doi: 10.1016/j.eplepsyres.2021.106650.

7. Beghi E, Carpio A, Forsgren L, et al. Recommendation for a definition of acute symptomatic seizure. Epilepsia. 2010 Apr; 51(4):671-5. doi: 10.1111/j.1528-1167.2009.02285.x.
8. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):522-30. doi: 10.1111/epi.13670.

9. World Health Organization [Internet]. Clinical management of COVID-19: interim guidance, 27 May 2020. Available from: https://apps.who.int/iris/handle/10665/332196.

10. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020;77(6):683-90. doi: 10.1001/jama-neurol.2020.1127.

11. Chou SH, Beghi E, Helbok R, et al. GCS-NeuroCOVID Consortium and ENERGY Consortium. Global Incidence of Neurological Manifestations Among Patients Hospitalized with COVID-19 – A report for the GCS-NeuroCOVID Consortium and the ENERGY Consortium. JAMA Netw Open. 2021;4(5):e2112131. doi: 10.1001/jamanetworkopen.2021.12131.

12. Desai I, Manchanda R, Kumar N, Tiwari A, Kumar M. Neurological manifestations of coronavirus disease 2019: exploring past to understand present. Neurol Sci. 2021;42(3):773-85. doi: 10.1007/s10072-020-04964-8.

13. Nalleballe K, Reddy Onteddu S, et al. Spectrum of neuropsychiatric manifestations in COVID-19. Brain Behav Immun. 2020;88:71-4. doi: 10.1016/j.bbi.2020.06.020.

14. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, et al. Neurologic manifestations in hospitalized patients with COVID-19: the ALBACOVID registry. Neurology. 2020;95(8):e1060-e70. doi: 10.1212/WNL.0000000000009937.

15. Asadi-Pooya AA, Simani L, Shahisavandi M, Barzegar Z. COVID-19, de novo seizures, and epilepsy: a systematic review. Neurol Sci. 2021;42(2):415-31. doi: 10.1007/s10072-020-04932-2.

16. Hepburn M, Mullaguri N, George P, et al. Acute symptomatic seizures in critically ill patients with COVID-19: is there an association? Neurocrit Care. 2021;34(1):139-43. doi: 10.1007/s12028-020-01006-1.

17. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. J Clin Virol. 2020;127:104362. doi: 10.1016/j.jcv.2020.104362.

18. Levi M. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol. 2020;7(6):e438-e40. doi: 10.1016/S2352-3026(20)30145-9.

19. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020;135(23):2033-40. doi: 10.1182/blood.2020006000.
INCIDENCija AKuTNIH SIMPTOMATSkiH NAPADAJA KOĐ BOLESNIKA S COVID-19: MONOCENTRIČNO ISTRAŽIVANJE

I. Šušak Sporiš, D. Sporiš, Z. Čolak Romić, P. Bago Rožanković i S. Bašić

Najčešći neurološki simptomi kod bolesnika s infekcijom SARS-CoV-2 su glavobolja, mialgija, encefalopatija, vrtoglavića, disgeuzija i anosmija, a čine više od 90% neuroloških manifestacija ove bolesti. Ostala neurološka zbivanja poput moždanog udara, poremećaja pokreta ili epileptičkih napada nisu česta, ali su potencijalno teške komplikacije s mogućim smrtnim ishodom. Primarni cilj ove studije bio je procijeniti učestalost akutnih simptomatskih napadaja kod bolesnika s COVID-19, dok je sekundarni cilj bio utvrditi njihovu moguću etiologiju. Od ukupno 5382 bolesnika hospitaliziranih u Kliničkoj bolnici Dubrava od 1. studenoga 2020. godine do 1. lipnja 2021. njih 38 (0,7%) je imalo akutne simptomatske napade. Od tih 38 bolesnika 29 (76,3%) ih je imalo novonastale epileptičke napade bez ranije anamneze epilepsije, dok je njih 9 (23,7%) imalo anamnezu dobro kontrolirane epilepsije uz pojavu epileptičkih napadaža tijekom bolesti COVID-19. Iako su akutni simptomatski napadaža rijetka komplikacija bolesti COVID-19, treba razmišljati o epileptičkim napadažima kod ovih bolesnika, osobito kod onih s teškim oblikom bolesti. Nakupljanje proupalnih citokina može doprinositi pojavu napadaža u bolesnika s COVID-19, ali takoder mogu biti posljedica primarnog zbivanja na mozgu uslijed bolesti COVID-19, poput moždanog udara ili encefalitisa.

Ključne riječi: Epileptički napadaži; Epilepsija; COVID-19; SARS-CoV-2