Recurrent Status Epilepticus and SARS-CoV-2 infection: the “perfect storm”

Giada Pauletto 1, Annacarmen Nilo 2, Cristian Deana 3, Lorenzo Verriello 1, Ilaria Del Negro 2,5, Christian Lettieri 1, Luigi Vetrugno 4, Mariarosaria Valente 2,5, Gian Luigi Gigli 2,5

1 Neurology Unit, Department of Neurosciences, S. Maria della Misericordia University Hospital, Udine, Italy; 2 Clinical Neurology Unit, Department of Neurosciences, S. Maria della Misericordia University Hospital, Udine, Italy; 3 Anesthesia and Intensive Care Unit, Department of Anesthesia and Intensive Care, S. Maria della Misericordia University Hospital, Udine, Italy; 4 Clinical Anesthesia and Intensive Care, Department of Medicine (DAME), University of Udine Medical School, Udine, Italy; 5 Department of Medicine (DAME), University of Udine Medical School, Udine, Italy

Abstract. Respiratory involvement is the most common clinical manifestation of COVID-19, but neurological symptoms and complications are increasingly being recognized. Seizures and status epilepticus (SE) have been described as possible consequences of hypoxia and metabolic derangements during SARS-CoV-2 infection, direct viral invasion of the central nervous system, or as para or post-infectious complications. Single episodes of SE have been described, occurring during the acute phase of COVID-19 or once the patients have been recovered. Herein, we present the case of a patient with a positive serology test for SARS-CoV-2 (IgG+, IgM-) and recurrent SE occurring within 36 days. Diagnostic work-up ruled out other known causes of SE. A post-COVID-19 infectious inflammatory/immune response is hypothesized as the possible trigger of SE. (www.actabiomedica.it)

Key words: Status epilepticus, SARS-CoV-2, EEG monitoring, anti-seizure medications, delirium.

Introduction

Novel coronavirus SARS-CoV-2, responsible for Coronavirus Disease (COVID-19) emerged in December 2019 in Wuhan, China, and rapidly developed into a global health emergency. Respiratory symptoms represent the most common clinical manifestation. Since the beginning of the pandemic, neurological involvement has been observed, mainly associated with a more severe disease form (1, 2). The most frequent neurological symptoms include: headaches (11–13%), dizziness (8–17%), confusion and altered consciousness (8–9%), acute cerebrovascular disease (3–5%), and seizures (0.5%). Lately, reports about COVID-19-related severe neurological para/post-infectious complications have been published (3). Single episodes of status epilepticus (SE) related to SARS-CoV-2 infection have been reported (4-9).

Herein, we describe a woman positive for anti-SARS-CoV-2 antibodies with recurrent new-onset SE characterized by different clinical features and increased drug-resistance.

Case report

A 63-year-old healthy woman was admitted to the Emergency Department (ED) of our University Hospital for fever (T 39°C) lasting for 10 days and diarrhea. During ED examination, the patient was wet, confused, and febrile (T 40°C). Vital parameters were as follows: heart rate 121 bpm, blood pressure 85/50 mmHg, and SpO2 95% while breathing room air.

Fluid challenge with normal saline was immediately started to restore normal blood pressure. Blood analysis revealed: leukopenia (2190/mm3) with low
neutrophil and lymphocyte counts (N 1690/mm$^3$, Ly 440/mm$^3$), thrombocytopenia (33000/mm$^3$), high levels of C-reactive protein (157 mg/L), D-dimers (65.588 FEUng/mL) and lactic dehydrogenase (1098 mmol/l), and mild renal insufficiency (1.41 mg/dl). Arterial gas analysis was unremarkable. Rapid serology testing was positive (IgG+, IgM-) for SARS-CoV-2, whereas the nasopharyngeal swab test was negative. A pulmonary CT scan showed diffuse pulmonary basal lobe opacifications. Blood and urine cultures were obtained, and empiric antibiotic therapy with meropenem and gentamycin was delivered. The patient was admitted to the COVID-19 intensive care unit (ICU) since an active SARS-CoV-2 infection could not be definitively excluded. Nevertheless, no subsequent repeated nasopharyngeal swabs or gastric tube samples confirmed an active COVID-19.

During ICU stay, she developed a further decrease in leukocytes and platelets, with coagulation tests indicating a diffuse intravascular coagulation (DIC). Blood and fresh frozen plasma transfusions were required. Microbiological cultures were all negative and no septic foci were found. Bone marrow aspirate excluded acute leukemia. After two days from ICU admission, the patient was sedated, intubated and put under mechanical ventilation because of worsening clinical conditions and incoming multiorgan failure. She was extubated three days later, but she presented mental confusion and unresponsiveness to external stimuli. EEG recording revealed a non-convulsive status epilepticus (NCSE), characterized by diffuse slow background activity with epileptiform discharges (spike-and-wave and sharp-and-slow-wave complexes) on bilateral fronto-polar and fronto-basal regions with right prevalence (Figure 1A).

The status epilepticus severity scale (STESS) rating was 3. A benzodiazepine I.V. bolus was ineffective, so I.V. levetiracetam (3000 mg daily) was started, with SE resolution after two days. Cerebral spinal fluid (CSF) examination was normal and negative for neurotropic viruses. Brain MRI was unremarkable. She remained in the ICU for 11 days, before being transferred to the Internal Medicine Unit. After 20 days, she was discharged home without any neurological sequelae.

Eleven days later, she was referred to the ED for worsening mental slowing and aphasia. She was afebrile and without any other symptoms. During ED staying, she developed a motor seizure, with right upper limb jerks evolving into a bilateral tonic-clonic seizure. Moreover, she appeared confused, partially oriented, and with a hypertonic and hyposthenic left lower limb. Laboratory tests and brain CT scan were unremarkable. EEG revealed sub-continuous epileptiform discharges on the right parietal region and the vertex, that spread to ipsilateral and contralateral temporal regions.

Figure 1. Electroencephalographic findings. First status epilepticus (SE): panel A showed a diffuse slow background activity, with high amplitude delta waves and spike-and-wave and sharp-and-slow-wave complexes on bilateral fronto-polar and fronto-basal regions with right prevalence. Second SE: panel B revealed a diffuse theta background activity with sub-continuous epileptiform discharges (sharp-waves and spikes) over the right parietal region and the vertex, that spread to ipsilateral and contralateral temporal regions.
Acta Biomed 2021; Vol. 92, N. 5: e2021208

A second CSF examination was performed, showing all normal parameters. Polymerase chain reaction (PCR) testing for SARS-CoV-2 and neurotropic viruses was negative, as well as a complete autoimmune panel for encephalitis, both on serum and CSF. The serology test for SARS-CoV-2 antibodies continued to be positive (IgG+, IgM-) and the nasopharyngeal swab was negative once more. Cytokine levels, in particular of IL-6 and IL-8, were mildly increased on serum and CSF. A whole-body positron emission tomography-computed tomography scan excluded occult neoplasms.

Since the patient was still on levetiracetam at highest dosage (3000 mg daily), she was treated with I.V. lacosamide 200 mg bid. Motor signs ceased, whereas confusion persisted and psychiatric symptoms appeared: behavioral disturbances, persecutory ideation, and aggressiveness. Levetiracetam was withdrawn, and treatment with valproic acid (30 mg/kg/day) and dexamethasone (16 mg/day) was started. Six days later, the patient clinically improved. EEG monitoring showed SE resolution. A control brain MRI performed 16 days later was negative (Figure 2C-D).

The patient was discharged home after 34 days: she was alert, oriented to herself, able to follow commands, and compliant with no focal neurological deficits, she appeared only repetitive and fatuous. She was still under lacosamide 200 mg bid and valproic acid 1250 mg daily. Forty-five days after being discharged, she was slightly improved. She did not experience any further seizures. A new EEG was performed, showing a mild diffuse slowing, without any epileptiform activity.

Discussion

Since the onset of COVID-19 pandemic, a growing number of case reports and series describe a wide array of neurological manifestations in the context of active SARS-CoV-2 infection or in the para/post-infectious phase (1, 2). Recently, SE cases associated with COVID-19, with or without encephalitis, have also been reported (4-10).

Here, we describe a woman presenting recurrent SE as a possible expression of a COVID-19 related encephalopathy. In both episodes, SE etiology remained otherwise unknown: metabolic encephalopathy, viral encephalitis, cerebral thrombosis and vasculitis, paraneoplastic encephalopathies, and known autoimmune encephalitides could all be ruled out. However, serum positivity for anti SARS-CoV-2 antibodies suggests that the recurrent SE may be a possible post-infectious neurological manifestation.

Different patterns of seroconversion have been described, the most common being IgM seroconversion occurring later than that of IgG. IgG detection in patients’ blood samples reaches 100% approximately 17–19 days after symptom onset, whereas IgM reaches a peak of 94.1% after 20–22 days.

One possibility is that our patient developed a more rapid IgG antibody response since IgM antibodies were never detected. However, the second analysis was performed more than 2 months after the first, and by that time IgM could have already decreased.
The absence of a positive nasal or gastric swab does not exclude a SARS-CoV-2 infection. In clinical practice, many patients with clear symptoms of COVID-19 demonstrate multiple negative PCR tests for SARS-CoV-2. Indeed, numerous studies have pointed out the high prevalence of false negative results (11).

The second SE was characterized by neuropsychiatric manifestations, correlating with a neuroanatomical substrate in the bilateral frontal cortex. Without EEG monitoring, it would have been impossible to make a differential diagnosis between NCSE with neuropsychiatric symptoms and delirium – the latter being a possible acute manifestation of COVID-19 (12). The complete brain MRI normalization after 16 days is suggestive of cortical suffering induced by SE. This SE lasted longer and was more difficult to treat than the first. These aspects may reflect that a recurrent SE is intrinsically more prone to drug resistance.

Other authors have reported cases of SE as an expression of an autoimmune/inflammatory response related to COVID-19 (4-7, 9). In particular, Balloy et al. (9) described a NCSE in a COVID-19 patient, without underlying meningitis or encephalitis. Two further articles reported cases of SE as the first and only symptom of COVID-19 without respiratory manifestations (5, 8). Dono and co-workers (6) presented the case of a woman previously affected by COVID-19 pneumonia who developed SE after the acute phase. They hypothesized that the SE was an expression of an autoimmune COVID-19 related encephalitis, despite reporting no data on anti-SARS-CoV-2 antibodies (6).

Carrol and colleagues (4) described a patient who developed refractory SE (RSE) 50 days after recovering from severe SARS-CoV-2 pneumonia. They performed an extensive diagnostic workup that demonstrated elevated inflammatory markers and concluded that the RSE was the result of a post infectious inflammatory response.

In our patient, cytokine levels were mildly increased, both in serum and CSF. However, cytokine tests were only performed at the time of the second SE, so we cannot exclude whether high levels were already present during the first hospitalization.

Conclusions

Our case adds to and broadens the clinical descriptions of SE associated with COVID-19 and suggests the possibility of SE recurrence in patients with previous SE as clinical manifestation or consequence of SARS-CoV-2 disease.

SE out of the blue is not rare, thus COVID-19 should now be considered as part of the diagnostic workup for new-onset SE. Action to prevention SE recurrence should be taken into considerations, especially given the increased drug-resistance at SE relapse.

Author Contributions: Dr. Pauletto: conceptualization, methodology, data curation, data analysis and interpretation, writing-original draft preparation, writing – review & editing. Dr. Nilo: conceptualization, methodology, data curation, data analysis and interpretation, writing-original draft preparation, writing – review & editing. Dr. Deana: conceptualization, data curation, data analysis and interpretation, writing-original draft preparation, writing – review & editing. Dr. Deana: conceptualization, data curation, data analysis and interpretation, writing-original draft preparation, writing – review & editing. Dr. Del Negro: data analysis and interpretation, writing – review & editing. Prof. Valente: supervision, writing – review & editing. Prof. Gigli: supervision, writing – review & editing. Dr. Pauletto and Dr. Nilo equally contributed to this work.

Acknowledgements: We would like to thank Dr. Stephanie Parsley for the English revision of the manuscript.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

References

1. Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. Lancet 2020; 19(9): 767-83. Doi: 10.1016/S1474-4422(20)30221-0.
2. Deana C, Verriello L, Pauletto G, et al. Insights into neurological dysfunction of critically ill COVID-19 patients. Trends Anaesthesia Critic Care 2020; In press. Doi: 10.1016/j.tacc.2020.09.005.
3. Gigli GL, Vogrig A, Nilo A, et al. HLA and immunological features of SARS-CoV-2-induced Guillain-Barré...
syndrome. Neurol Sci 2020; 41(12): 3391-4. Doi: 10.1007/s10072-020-04787-7.
4. Carroll E, Neumann H, Aguero-Rosenfeld ME, et al. Post-COVID-19 inflammatory syndrome manifesting as refractory status epilepticus. Epilepsia 2020; 61(10): e135-e139. Doi: 10.1111/epi.16683.
5. Vollono C, Rollo E, Romozzi M, et al. Focal status epilepticus as unique clinical feature of COVID-19: a case report. Seizure 2020; 78: 109-112. Doi: 10.1016/j.seizure.2020.04.009.
6. Dono F, Carrarini C, Russo M, et al. New-onset refractory status epilepticus (NORSE) in post SARS-CoV-2 autoimmune encephalitis: a case report. Neurol Sci 2021; 42(1): 35-38. Doi: 10.1007/s10072-020-04846-z.
7. Chen W, Toprani S, Werbaneth K, Falco-Walter J. Status epilepticus and other EEG findings in patients with COVID-19: a case series. Seizure 2020; 81: 198-200. Doi: 10.1016/j.seizure.2020.08.022.
8. Somani S, Pati S, Gaston T, Chitlangia A, Agnihotri S. De novo status epilepticus in patients with COVID-19. Ann Clin Transl Neurol 2020; 7(7): 1240-4. Doi: 10.1002/can.3.51071.
9. Balloy G, Leclair-Visonneau L, Péréon Y, Magot A, Peyre A, Mahé PJ, et al. Non-lesional status epilepticus in a patient with coronavirus disease 2019. Clin Neurophysiol 2020; 131(8): 2059-61. Doi: 10.1016/j.clinph.2020.05.005.
10. Pilotto A, Odolini S, Masciocchi S, et al. Steroid-responsive encephalitis in coronavirus disease 2019. Ann Neurol 2020; 88(2): 423-7. Doi: 10.1002/ana.25783.
11. Arevalo-Rodriguez I, Buitrago-Garcia D, Simancas-Racines D, et al. False-negative results of initial RT-PCR assays for COVID-19: a systematic review. PLoS One 2020; 15(12): e0242958. Doi: 10.1371/journal.pone.0242958.
12. Hosseini AA, Shetty AK, Sprigg N, Auer DP, Constantinescu CS. Delirium as a presenting feature in COVID-19: neuroinvasive infection or autoimmune encephalopathy? Brain Behav Immun 2020; 88: 68-70. Doi: 10.1016/j.bbi.2020.06.012.

Correspondence:
Received: 20 March 2021
Accepted: 9 April 2021
Annacarmen Nilo
Clinical Neurology Unit, Department of Neurosciences, Santa Maria della Misericordia University Hospital, Italy
Piazzale S. Maria della Misericordia 15, Udine (UD), 33100
Phone: 0039-0432559020/0039-3476052819
E-mail: annacarmen.nilo@gmail.com