Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Clinical letter

Anti-NMDA receptor encephalitis presenting as new onset refractory status epilepticus in COVID-19

Giulia Monti, Giada Giovannini, Andrea Marudi, Roberta Bedin, Alessandra Melegari, Anna Maria Simone, Mario Santangelo, Alessandro Pignatti, Elisabetta Bertellini, Tommaso Trenti, Stefano Meletti

Neurology Unit, Ospedale Ramazzini di Carpi, AUSL di Modena, Italy
Neurology Unit, OCB Hospital, Azienda Ospedaliera Universitaria di Modena, Italy
Department of Biomedical, Metabolic, and Neural Science, University of Modena and Reggio Emilia, Modena Italy
PhD Program in Clinical and Experimental Medicine, University of Modena and Reggio Emilia, Modena, Italy
Intensive Care Unit, OCB Hospital, Azienda Ospedaliera Universitaria di Modena, Italy
Diagnostica patologie autoimmuni - Dipartimento Interaziendale ad Attività Integrata di Medicina di Laboratorio ed Anatomia Patologica, Azienda Ospedaliera Universitaria di Modena, Italy
Intensive Care Unit, Ospedale Ramazzini di Carpi, AUSL di Modena, Italy

ARTICLE INFO

Keywords:
NORSE
Anti-NMDA-R encephalitis
COVID-19
Status epilepticus
Autoimmune diseases

1. Introduction

During the outbreak of coronavirus disease 2019 (COVID-19) clinicians are increasingly involved in the observation of possible neurological complications due to the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Among neurologic emergencies, new onset seizures and status epilepticus in non-epileptic patients are up to now, infrequently reported [2].

We hereby report a case of New Onset Refractory Status Epilepticus (NORSE) [3] in a patient with anti-NMDA receptor encephalitis and concomitant SARS-CoV-2 infection.

2. Case report

A 50-year-old man, with no significant pathology in his medical history except for mild hypertension, employed as a health care worker in the ambulance emergency service, presented on February 23rd an acute onset of psychiatric symptoms (confabulations and delirious ideas). He had fever (T 38 °C) without increased CRP or leucocytosis, respiratory symptoms (in particular no cough, cold or dyspnea) or diarrhea. After 4 days, focal motor seizures with impaired awareness and oro-facial dyskinesia/automatisms appeared. A first brain MRI was negative. He was treated with diazepam followed by adequate doses of valproic acid and lacosamide. Nevertheless, he suddenly developed a refractory status epilepticus (RSE) requiring admission to the intensive care unit (ICU) and anesthetics' treatment (Fig. 1).

In the first week the patient underwent two spinal-taps with a CSF finding of 76 and 25 cells respectively plus oligoclonal bands. Search for the main neurotropic fungi, bacteria and viruses (and in particular for herpes viruses) was negative. On the other hand, anti-NMDA receptors antibodies positivity on CSF was found, while it was negative in serum (Table 1). A second brain MRI was unremarkable. Due to the rapid spread of COVID-19 cases in our district and in relation to the high occupational risk of the patient, on March the 3rd a throat swab for SARS-CoV-2 was acquired. Real-time reverse-transcription polymerase chain reaction analysis (PCR) confirmed SARS-CoV-2 infection. No sign on interstitial pneumonia were present on chest radiography and CT scan. The patient was then transferred to an ICU dedicated to COVID-19.
patients.

Therapeutic management was based on immunomodulating therapies typically used for anti-NMDA receptors antibodies encephalitis (metilprednisolone, IGIV, plasma-exchange) together with antiseizure drugs/anesthetics to control refractory/super refractory status (SRSE), (metilprednisolone, IGIV, plasma-exchange) together with antiseizure medications (ASM = anti-seizures medications; BRV = brivaracetam; HCLQ = hydroxychloroquine; IGIV = intravenous immunoglobulins; LCM = lacosamide; LPV/r = lopinavir/ritonavir; MDZ = midazolam; KETA = Ketamine; PB = phenobarbital; PER = perampanel; PEX = plasma exchange; PRO = propofol; RSE = refractory status epilepticus; SRSE = super-RSE; VPA = valproate).

Fig. 1. Temporal evolution of the condition in relation to diagnostic findings and treatments. Pictorial evolution of the condition from February 23rd to April 30th 2020.

3. Discussion

This is, to our knowledge, the first NORSE reported in a patient with co-infection with SARS-CoV-2 infection. Regarding the association between SARS-CoV-2 infection and the development of autoimmune encephalitis, the case described does not allow to attribute a definite pathogenetic role to COVID-19. Indeed, the patient could have been an asymptomatic carrier of SARS-Cov-2 and had an unrelated anti NMDA receptor encephalitis. However, very recently another case report of anti-NMDA receptor encephalitis in COVID-19 with prominent psychosymmetric symptoms has been published [4]. In our patients, the clinical onset characterized by fever, psychiatric disorders, and seizures, immediately oriented clinicians to investigate an autoimmune encephalitis, once a viral infection was excluded on the basis of CSF PCR negativity for the main neurotropic viruses. The patient had no interstitial pulmonary involvement, both at the beginning of the clinical history and during the evolution. Indeed, the search for SARS-CoV-2 infection was done mainly on the basis of the rapid increase in COVID-19 outbreak (the first COVID-19 patient was recorded on February 25 in Modena province), and on the high occupational risk of the patient. Anti-NMDA receptor encephalitis after infection with herpes simplex virus (HSV1) is a well know condition. A prospective study show that autoimmune encephalitis occurred in 27 % of patients with herpes simplex encephalitis [5]. In these cases, however, the development of autoimmune encephalitis is observed a few days, or more often weeks, after the end of the viral infection, and not concomitantly with it, as in our case. However, it is also not possible to exclude that SARS-CoV-2 infection played a role in the genesis of the autoimmune encephalitis in our patient, and only subsequent observations of cases with similar features can answer this question. Indeed, it is not possible to exclude a role of the so-called “cytokines storm”, often associated to COVID-19 infection, to maintain and promote refractory or super-refractory status epilepticus. IL6 is known to be elevated during the inflammatory phase of COVID infection. Moreover, increased CSF IL6 levels have been recognized to facilitate intrathecal autoantibody production in anti-NMDAR encephalitis [6]. As previously reported, IL6 and IL8 are both inflammatory cytokines/chemokines that have been found increased in CSF of patients with NORSE and febrile infection-related epilepsy syndrome (FIRES) where it could be speculated if their raise is the cause or the effect of SE [7].
A last but not less important aspect is that this case is paradigmatic to underline the importance of doing ‘whatever it takes’ and never give-up even if the clinical situation appears to be particularly difficult in young and healthy patients with NORSE.

Standard protocol approvals, registrations, and patient consents

The scientific advisory boards of our institution approved the research report. Written informed consent has been obtained from patient’s relative.

Data availability

Anonymized data will be shared by request of any qualified investigator.

Ethical publication statement

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure statement

Dr. Giovannini, Monti, Simone, Melegari, Bedin, Marudi, Pignatti, Bertellini, and Dr. Santangelo reports no disclosures. Prof. Meletti received research grant support from the Ministry of Health (MOH); has received personal compensation as scientific advisory board member for UCB and EISAI.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2020.07.006.

References

[1] Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020. https://doi.org/10.1001/jama neurol.2020.1127. Published online April 10.
[2] Lu L, Xiong W, Liu D, Liu J, Yang D, Li N, et al. New onset acute symptomatic seizure and risk factors in Corona Virus Disease 2019: a retrospective multicenter study. Epilepsia 2020. https://doi.org/10.1111/epi.16524.
[3] Gaspard N, Hirsch LJ, Sculier G, Lindenkemper T, van Baalen A, et al. New-onset refractory status epilepticus (NORSE) and febrile infection-related epilepsy syndrome (FIRES): state of the art and perspectives. Epilepsia 2018;59:745-52.
[4] Panariello A, Bassetti R, Radice A, Rossotti R, Pozzi M, et al. Anti-NMDA receptor encephalitis in a psychiatric Covid-19 patient: a case report. Brain Behav Immunol 2020;87:179-81.
[5] Armangue T, Spataola M, Vlagaos A, Mattozzi S, Carceles-Cordon M, et al. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. Lancet Neurol 2018;17:760-72.
[6] Byun J-J, Lee S-T, Moon J, Jung JH, Sunwoo JS, Lim JA, et al. Distinct intrathecal interleukin-17/interleukin-6 activation in anti-N-methyl-D-aspartate receptor encephalitis. J Neuroimmunol 2016;297:141-7. Eur Cytokine Netw. 2019. 4:130-134.
[7] Sakuma H, Tanuma N, Kuki I, Takahashi Y, Shiomi M, et al. Intrathecal over-production of proinflammatory cytokine and chemokines in febrile-infection related status epilepticus. J Neurol Neurosurg Psych 2015;86:820–2.
[8] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395(10229):1033–4.