Focal seizures with impaired awareness as long-term neurological complication of COVID-19: a case report

Bozzali, Marco, Grassini, Alberto, Morana, Giovanni, Zotta, Michela, Cabras, Sara, Romagnolo, Alberto, Artusi, Carlo Alberto, Montalenti, Elisa, Rizzone, Mario Giorgio, Garbossa, Diego, Montanaro, Elisa, Cercignani, Mara and Lopiano, Leonardo (2021) Focal seizures with impaired awareness as long-term neurological complication of COVID-19: a case report. Neurological Sciences, 42. pp. 2619-2623. ISSN 1590-1874

This version is available from Sussex Research Online: http://sro.sussex.ac.uk/id/eprint/99217/

This document is made available in accordance with publisher policies and may differ from the published version or from the version of record. If you wish to cite this item you are advised to consult the publisher's version. Please see the URL above for details on accessing the published version.

Copyright and reuse:
Sussex Research Online is a digital repository of the research output of the University.

Copyright and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable, the material made available in SRO has been checked for eligibility before being made available.

Copies of full text items generally can be reproduced, displayed or performed and given to third parties in any format or medium for personal research or study, educational, or not-for-profit purposes without prior permission or charge, provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.
FOCAL SEIZURES WITH IMPAIRED AWARENESS AS LONG-TERM NEUROLOGICAL COMPLICATION OF COVID19: A CASE REPORT

Neurological Sciences – Brief Communication

Keywords: COVID-19; Epilepsy; Focal seizures with impaired awareness; Encephalitis

References: 11

Figures: 2 (colour)
FOCAL SEIZURES WITH IMPAIRED AWARENESS AS LONG-TERM NEUROLOGICAL COMPLICATION OF COVID19: A CASE REPORT

Marco Bozzali, MD¹,²; Alberto Grassini¹, MD; Giovanni Morana¹, MD; Michela Zotta³, MD; Sara Cabras¹, MD; Alberto Romagnolo¹, MD; Carlo Alberto Artusi¹, MD; Elisa Montalenti⁴, MD; Mario Giorgio Rizzone¹, MD; Diego Garbossa¹, MD; Elisa Montanaro⁴, PsyD; Mara Cercignani², PhD; Leonardo Lopiano, MD, PhD¹,⁴

Author Affiliations:
¹ Department of Neuroscience “Rita Levi Montalcini”, University of Torino, Via Cherasco 15, 10126, Torino, Italy.
² Department of Neuroscience, Brighton & Sussex Medical School, University of Sussex, Brighton, East Sussex, United Kingdom.
³ Department of Diagnostic Imaging, Nuclear Medicine Unit, A.O.U. Città della Salute e della Scienza di Torino, Torino, Italy
⁴ Neurology 2 Unit, A.O.U. Città della Salute e della Scienza di Torino, 10124, Torino, Italy.

Corresponding Author:
Prof. Marco Bozzali, ‘Rita Levi Montalcini’ Department of Neuroscience, University of Torino, Via Cherasco, 15, 10126 Torino, Italy. Telephone number: +39 011.6709366; E-mail address: marco.bozzali@unito.it.

Authors’ contribution:
M.B., A.G. and L.P. planned all clinical and instrumental investigations, interpreted the results, and wrote the first draft of the manuscript.

G.M. and M.C. supervised MRI acquisition and contributed to data interpretation.

M.Z. supervised PET imaging and contributed to data interpretation.

A.R., M.G.R., C.A.A., D.G. and S.C. performed clinical assessments and managed all serological and CSF examinations.

E. Montal. contributed to interpretation of neurophysiological data.

E. Montan. did neuropsychological testing.

All Authors were involved in drafting or revising the manuscript.
Funding:
None.

Potential Conflicts of Interest:
On behalf of all authors, the corresponding author declares that there is no conflict of interest.

Ethical standards:
The patient provided written consent. All procedures were performed in accordance with the local ethics committee and with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Data availability
MB and AG have full access to all data presented in the study and take responsibility for their integrity and for the accuracy of data analysis.
Abstract

We report here the first case of a young individual otherwise healthy, who presented with frequent focal seizures with impaired awareness as a possible long-term complication of severe-acute-respiratory-syndrome-coronavirus-2 infection. Seizures were documented by electroencephalography and responded clinically and neuro-physiologically to antiseizure therapy. The patient underwent an extensive investigation including cerebrospinal-fluid examination, conventional and quantitative brain Magnetic Resonance Imaging and 18-FDG Positron-Emission-Tomography. Beyond the clinical interest, this case contributes to clarify the possible pathways by which SarsCOV2 may enter the Central Nervous System and cause long-term neurological complications.

Introduction

First-ever occurrence of seizures in non-epileptic individuals have been described in the acute phase of severe-acute-respiratory-syndrome-coronavirus-2 (SARS-CoV-2) infection\(^1\). In these cases, possible underlying mechanisms include metabolic or fever induced brain dysfunction, cytokine-storm damage, brain vessel endothelial infarction, autoimmunity, or Central-Nervous-System (CNS) viral invasion\(^2\). We report here the case of a young individual with no remarkable medical history who presented with frequent focal seizures with impaired awareness newly arisen two months after resolution of their Coronavirus-disease-2019 (COVID-19) acute phase.

Case report

A 54-year old lady working as a nurse in a COVID19-Ward received, at the end of March 2020, her first-ever SARS-CoV-2 nasopharyngeal-swab after reporting a high-risk contact with a colleague suffering from COVID-19. Despite a negative outcome, five days later she started complaining of fever, nasal congestion, throat pain, fatigue, shortness of breath, muscle- and joint-pain, diarrhoea, anosmia, ageusia. These symptoms persisted for 4 weeks while she remained at home in precautionary isolation. At the end of April 2020, she recovered from all symptoms with the exception of fatigue, muscle- and joint-pain, anosmia, and ageusia. Concomitantly, she started complaining of continuous headaches and feeling of gait unbalance. She was admitted to the Emergency-Ward of the University Hospital of Turin, and received full-blood and arterial-blood oxygenation tests (all parameters in normal range), Chest X-rays (normal), and Real-Time PCR on
nasopharyngeal-swab (positive for SarsCOV2). Due to her clinical stability she was discharged, and remained at home in quarantine until she resulted negative on two consecutive SarsCOV2 swab-tests. She was serologically tested for antibodies anti-SarsCOV2, resulting IgG positive and IgM negative. Clinically, she kept complaining of fatigue, gait unbalance and headaches. In June 2020, she underwent a brain MRI scan, showing minimal non-specific white matter hyperintensities on T2-weighted images. In July 2020, she started complaining of frequent (6-8 times a day) short episodes (about 1 min duration each) of olfactory hallucinations (described as “burning rubber smell”) followed by 10-15 min intervals of detachment from reality (described as “mental confusion”). In Mid-September 2020, she was admitted to our Neurology Unit (Department of Neuroscience, University of Turin, Italy) for investigation. On examination, there were no obvious impairments in her higher-level functions; cranial nerves were intact; there was no weakness at any limb; muscular tone was normal; reflexes were symmetrical, and plantars down-going bilaterally; coordination tests were well performed; there were no sensory deficits; her gait was normal. A mild right-deviation was observed on the Unteberger test. She underwent an Electroencephalogram (EEG) demonstrating the presence of focal slow-waves alongside sharp-spikes in the fronto-temporal areas bilaterally (Figure 1A). Repetition of SarsCOV2 nasopharyngeal-swab was negative, while serum specific SarsCOV2 IgG remained highly positive (140 U/ml). Blood tests, including vitamin B12, folates, thyroid-function tests were normal. Serological analysis to exclude autoimmune diseases and systemic infection resulted negative. A new brain MRI scanning at 3T, including high-resolution conventional acquisitions (FLAIR, T1-, T2-weighted, Susceptibility-Weighted-Imaging and post-contrast T1-weighted images), confirmed prior non-specific white matter changes (no additional abnormalities) (Figure 1C-G). CSF examination revealed a slight increase of proteins (55mg/dl) with normal cell count. CSF polymerase-chain-reaction (PCR) for detection of common neurotropic pathogens (i.e., Herpes Simplex 1 and 2, Human Herpes 6, Enterovirus, Human Paraechovirus, Varicella Zoster, Cytomegalovirus, Streptococcus Pneumoniae, Neisseria Meningitidis, Haemophilus Influenzae, Streptococcus Agalactiae, Listeria Monocytogenes, Escherichia Coli K1, Criptococcus Neoformans) and for SarsCOV2 returned negative results. Immunoelectrofocusing did not reveal any oligoclonal bands. No specific antibodies anti-SarsCOV2, neither brain autoimmune (anti NMDA glutamate receptor, AMPA 1 and 2 glutamate receptor, GABA receptor, LG1, CASPR2, DPPX, Thyroperoxidase, Thyroglobulin, TSH receptor) or paraneoplastic antibodies (anti YO, Sox1, Zic4, Titin, Hu,
GAD65, CV2, Ri, Ma2, Retin, Amphiphysin, Tr) were identified on the CSF. Considering the feeling of gait unbalance and deviation on the Untheberger test, she underwent also brainstem-auditory-evoked-potentials (BAEP) showing a mild bilateral increase of latencies. An extensive neuropsychological assessment revealed an isolated impairment of frontal-executive functions (Frontal-Assessment-Battery corrected score=12.3). For this reason, the patient underwent a brain $[^{18}F]$FDG-Positron-Emission-Tomography that resulted normal (Figure 1H-L). She was started on Levetiracetam therapy with only partial benefit, and then shifted to Carbamazepine, 400 mg twice a day. After being on Carbamazepine for 12 weeks, the patient reported clear improvement of symptoms with “burning sensation”(3) in her nose (instead of smell hallucinations) occurring with reduced frequency (2 times a week) alongside shorter intervals of detachment from reality. Moreover, EEG repetition did no longer show any spikes and revealed reduction of slow-waves (Figure 1B).

Discussion
Since COVID19 became clinically overt, the patient presented with a clinical progression that fits with a subacute encephalitis (Figure 2). Despite lack of evidence of SarsCOV2 RNAs in the CSF, the clinical evolution indicates a plausible anatomical pathway by which SarsCOV2 may have sub-acutely infected the central-nervous-system (CNS). Being primarily a respiratory virus, there are at least two possible ways for SarsCOV2 to invade the CNS, through an hematogenous or an axonal route(4). In the latter case, SARS-CoV-2 is supposed to infect the axonal terminations and actively translocate backwards into the CNS. The neuronal fibres that are most likely infected by SarsCOV2 are those of the olfactory nerves, as suggested by anosmia as typical symptom of COVID19, and supported by radiological evidence(5). Another possible route is trough other cranial nerves with invasion of the brainstem, as partially supported by our clinical (Unterberger test) and neurophysiological (BAEP) observations. Evidence of paracellular transmigration of Betacoronaviruses (e.g., SARS-CoV-1) has been provided in animal studies, with viral demonstration within the olfactory bulb, piriform cortex, hippocampus and temporo-mesial cortex, thalamus, brainstem nuclei[6-7]. Importantly, persistence of coronavirus RNAs in the CNS was demonstrated long time after acute encephalitis(8). In our patient, we were unable to detect viral RNAs in the CSF. This might be due to the long interval elapsed between the acute COVID19 phase and CSF examination. Consistently, it was previously shown that SarsCOV2 RNAs are detectable in the CSF of a small percentage of COVID19 patients with neurological symptoms(9), often requiring repeated
CSF examination\(^{(10)}\). Nonetheless, our patient developed focal seizures with impaired awareness (documented by EEG) responding to antiseizure medication. In contrast to previous reports in acute cases\(^{(10-11)}\), we could not demonstrate abnormalities in the temporo-mesial cortex, which -we argue- might no longer be detectable in post-acute COVID19 stages. On neuropsychological assessment, our patient showed an isolated deficit of executive functions, whose relationship with SarsCOV2 infection remains to be clarified despite a suggestive anatomical overlap with fronto-temporal seizures.

In conclusion, we report here a case of fronto-temporal epilepsy, possibly related to SarsCOV2 infection. This diagnosis of causality, which remains speculative, is based on exclusion assessments and clinical elements supporting such an hypothesis (clinical evolution, EEG alterations; response to antiseizure medication).

We expect this sort of long-term complications requiring immediate identification and treatment to become increasingly frequent in the future.
References

1. Mao L, Wang M, Chen S, et al (2020) Neurological Manifestations of hospitalized Patients with COVID-19 in Wuhan, China: a retrospective case series study. JAMA Neurol. https://dx.doi.org/10.1001%2Fjamanenurol.2020.1127
2. Asadi-Pooya AA (2020) Seizures associated with coronavirus infections. J Seizure. https://dx.doi.org/10.1016%2Fj.seizure.2020.05.005
3. Heo K, Kim KM, Han SM et al (2020). Nasal pain as an aura: Amygdala origin? Seizure 2020. https://doi.org/10.1016/j.seizure.2020.09.028
4. Mishra R, Banerjea A (2020) Neurological damage by coronaviruses. Front. Immunol. https://dx.doi.org/10.3389%2Ffimmu.2020.565521
5. Laurendon T, Radulesco T, Mugnier J, et al (2020) Bilateral transient olfactory bulb edema during COVID-19-related anosmia. Neurology. https://doi.org/10.1212/wnl.0000000000009850
6. Pearlman S, Jacobsen G, Afifi A (1989) Spread of a Neurotropic Murine Coronavirus into the CNS via the Trigeminal and Olfactory Nerves. Virology. https://dx.doi.org/10.1016%2F0042-6822(89)90446-7
7. McCray PB, Pewe L, Wohlford-Lenane C, et al (2007) Lethal infection of K18-hACE2 mice infected with severe acute respiratory syndrome coronavirus. J. Virol. https://doi.org/10.1128/jvi.02012-06
8. Jacomy H, Fragoso G, Almazan G, et al (2006) Human coronavirus OC43 infection induces chronic encephalitis leading to disabilities in BALB/C mice. Virology. https://doi.org/10.1016/j.virol.2006.01.049
9. Neumann B, Schmidbauer ML, Dimitriadis K, et al (2020) Cerebrospinal fluid findings in COVID-19 patients with neurological symptoms. J. Neurol. Sci. https://dx.doi.org/10.1016%2Fj.jneurolsci.2020.117090
10. Virhammar J, Kumlien E, Fällmar D, et al (2020) Acute necrotizing encephalopathy with SARS-CoV-2 RNA confirmed in cerebrospinal fluid. Neurology. https://doi.org/10.1212/WNL.0000000000010250
11. Moriguchi T, Harii N, Goto J, et al (2020) A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis. https://doi.org/10.1016/j.ijid.2020.03.062
Figure legend:

Figure 1

The first EEG, recorded before therapy initiation, showed a pattern of focal slow activity and spikes in the fronto-temporal area bilaterally (abnormalities magnified in red squares) (A). The second EEG, performed 4 weeks after initiation of antiseizure
medication, did no longer reveal any pathological alteration (B). EEG recordings were performed with scalp electrodes placed according to the International 10-20 system with bipolar montage; Brain MRI at the level of the centrum semiovale demonstrated only few hyperintense foci on FLAIR (C), mildly hypointense on T1-weighted images (D) with no contrast-enhancement (CE) on corresponding CE T1-weighted images (E). These abnormalities keep with minimal non-specific changes (arrow, C-E). Co-registered FLAIR (F,G), 18F-FDG PET (H, L) and fused PET/MRI FLAIR images (I) did not show any temporal lobe abnormalities, with physiological tracer uptake according to patient’s age.

Figure 2

The picture summarizes the clinical evolution of Sars-COV2 infection in the presented case alongside findings from the most relevant laboratory and instrumental examinations. See text for further details.
