Neuropsychiatric manifestations in a patient with prolonged COVID-19 encephalopathy: case report and literature review

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Abstract
While the respiratory complications of COVID-19 infection are now well known, psychiatric manifestations are an emerging issue. We report a case of prolonged encephalopathy secondary to COVID-19 which was associated with prominent neuropsychiatric features. The patient went on to develop sub-clinical seizures, a rare but recognised complication of SARS-CoV-2.

Keywords: COVID-19; delirium; encephalopathy

Introduction
The newly identified SARS-associated coronavirus (SARS-CoV2) emerged in Wuhan, China, in late 2019, and rapidly spread globally (Wuhan Municipal Health Commission, 2020; Lu et al. 2020; Hui et al. 2020; Paules et al. 2020). Coronavirus disease (COVID-19) was declared a pandemic by the World Health Organisation (WHO) on March 11 2020 (WHO, 2020). The first confirmed case of coronavirus in the Republic of Ireland was announced on the 29 February 2019 (Irish NPHET Statement, 2020).

High rates of anxiety, depression, post-traumatic stress disorder, distress and stress have been reported in the general population during the COVID-19 pandemic, (Kelly, 2020). Risk factors specific to distress include the presence of psychiatric or chronic illness (Xiong et al. 2020). Other than prior psychiatric disorder, those with greater levels of pandemic-related disruption in daily life are more likely to show signs of depression, anxiety and trauma-related symptoms (Sherman et al. 2020).

COVID-19 has been shown to be associated with an increased incidence of first psychiatric disorder up to 3 months after diagnosis, while a previous psychiatric diagnosis may be an independent risk factor for COVID-19 diagnosis (Taquet et al. 2021). A large study of 40,469 COVID-19 adult patients found that 22.5% had neuropsychiatric manifestations. While the most common included anxiety and related disorders (4.6%), a broad range of presentations including sleep disorders, affective disorders, psychosis, encephalopathy and seizure were noted (Nalleballe et al. 2020).

A UK-based surveillance project of neuropsychiatric and neurological complications of SARS-CoV-2 found that in COVID-19 patients with altered mental state, 92% of these were new diagnoses of neuropsychiatric disorders. New-onset psychosis, neurocognitive syndrome and affective disorders were recorded, (Varatharaj et al. 2020).

In patients presenting with COVID-19, it is estimated that 36% will have neurological symptoms, including impaired consciousness, dizziness, headache and neuromuscular dysfunction (Mao et al. 2020). A study of critically ill patients with COVID-19 found that 74% had COVID-19 related encephalopathy and common MRI findings were diffuse deep white matter, corpus callosum and basal ganglia T2/FLAIR hyperintensity (Scullen et al. 2020). An analysis of case reports and case series suggested that encephalopathy is more common in patients of 50 years or more and is more common in critically ill patients (Garg et al. 2020). However, in most patients, cerebral spinal fluid (CSF) does not demonstrate evidence of encephalitis. Although SARS-CoV-2 RNA can be detected in CSF with polymerase chain reaction (PCR) testing (Huang et al. 2020), repeated negative CSF has been associated with subclinical seizures (Berner-Valnet et al. 2020; Volleno et al. 2020; Somani et al. 2020; Balloy et al. 2020), little attention has been paid to the neuropsychiatric presentation of these cases.

While there are several case reports of patients with COVID-19-related encephalopathy with associated subclinical seizures (Berner-Valnet et al. 2020; Volleno et al. 2020; Somani et al. 2020; Balloy et al. 2020), little attention has been paid to the neuropsychiatric presentation of these cases.

In this case report, we present a case of prolonged encephalopathy secondary to COVID-19 which was associated with prominent neuropsychiatric features.

Case
A 56-year-old White Irish male presented to the Emergency Department of Beaumont Hospital, a large Dublin academic teaching hospital, complaining of chest pain, shortness of breath and cough, 2 weeks after the first COVID-19 case was diagnosed in Ireland. His past medical history included hypertension, hypercholesterolaemia and drug-induced hepatitis (from a prescribed antibiotic). He was apyrexic and normotensive with a respiratory
rate of 20. Sp02 was 94% on room air. The patient was alert and coherent.

C-Reactive Protein (CRP) was raised at 54 mg/L (normal range <10 mg/L) while other inflammatory markers were within normal ranges. Electrocardiogram was unremarkable. Troponin level was 15 ng/L and 14 ng/L on serial data (normal range <14 ng/L). A coronary angiogram showed no obstructive coronary disease. CT Thorax with contrast showed multifocal mucous plugging with subadjacent foci of peribronchovascular nodularity and ground-glass change. SARS-CoV2 PCR nasopharyngeal swab was negative. The patient was treated for community-acquired bacterial pneumonia with IV amoxicillin and was discharged with a prescription for a further 5 days of oral amoxicillin.

The patient represented to the Emergency Department 6 days later, with confusion, agitation and complaining of ‘pressure in the head’. His family gave a collateral of rapidly progressive disorientation, forgetfulness and difficulty using his phone, driving and performing complex tasks. The patient had a good functional and cognitive baseline. He was employed on a full-time basis in a skilled job.

On examination, he was amnestic with executive dysfunction, significant attentional deficits, and poor spatial awareness. There were no localising sensorimotor findings. Vitals showed pyrexia – 38.5°, heart rate of 96 bpm, normotensive blood pressure, respiratory rate between 16–22/minute and Sp02 of 96% on room air. SARS-CoV2 PCR nasopharyngeal swab was positive. The patient underwent a sequence of investigations in order to reach a definitive diagnosis as to the cause of his acute neurological presentation. CSF revealed <1/µl leucocytes, <1/µl erythrocytes, glucose of 2.9 mmol/L and total protein of 35. CSF PCR was negative for herpes simplex type 1 (HSV-1), herpes simplex type 2 (HSV-2), varicella zoster virus (VZV), parechovirus (HPeV) and mumps virus RNA. Paraneoplastic antibody screen was negative (anti-Hu, Yo, Ri, Ma, CV2, PNMA2, MA2TA, recoverin, TITIN, SOX1 ZIC4, GAD65, Tr (DNER), amphiphysin). Anti-N-methyl D-aspartate (NMDA) antibodies were negative. Autoimmune screen and vasculitic screen were negative. Frontotemporal dementia screen of CSF tau, phospho-tau and beta-amyloid were within normal ranges. Ammonia and copper levels were within normal ranges. Electroencephalogram (EEG) showed normal background rhythm with no focal or generalised epileptiform discharges. Magnetic Resonance Imaging (MRI) Brain showed non-specific subcortical FLAIR hyperintensities in the superior frontal lobes and parasagittal right frontal lobe at the vertex, suggesting a resolving toxic aetiology. On week 10 of admission, the patient was treated with Privigen IVig at a dose of 20 g for 5 consecutive days. The decision was made to trial IVlg in light of promising case reports emerging in the literature of treatment of COVID-encephalopathy. The patient was subsequently transferred to a step-down facility for neurorehabilitation at week 12 of admission, where he initially made good progress. The patient scored 24/30 in a MoCA prior to transfer.

Four weeks into his rehabilitation (16 weeks after his initial presentation), the patient deteriorated from a cognitive and psychiatric perspective. He again became disoriented and agitated, with increased non-purposeful motor activity. His speech was repetitive with increased flow. Short-term memory and working memory were impaired. He was re-admitted to Beaumont Hospital for further evaluation. The BHDP was utilised and regular haloperidol 2 mg BD was prescribed. SARS-CoV2 PCR nasopharyngeal swab was negative. Repeat lumbar puncture was unremarkable. Positron emission topography (PET) scan did not show signs of malignancy. MRI Brain showed no residual caudate or frontal lobe abnormalities. Due to the complex nature of the patient’s presentation, he underwent a right frontal lobe core biopsy, but no abnormalities were detected. Video EEG showed bi-frontal periodic epileptiform discharges. The patient remained alert but apathetic throughout the EEG. Bolus administration of lorazepam significantly improved alertness and prosody of speech, with resolution of frontal discharges. This finding confirmed sub-clinical seizures, that is, seizures recorded on EEG without motor or somatic seizure activity (Zangaladze et al. 2008).

The patient showed clinical improvement with introduction of anti-epileptic drugs; levetiracetam 750 mg BD, and clobazam 10 mg BD. A subsequent EEG showed complete resolution of the epileptiform discharges. Some 2 months after his readmission, he scored 26/30 on the MoCA, losing points for visuospatial executive functioning and delayed recall. In addition, he scored 88/100 on the Addenbrooke’s Cognitive Assessment (ACE-III) (Hsieh et al. 2013), losing points in visuospatial abilities, language, and attention. The diagnosis of COVID-19 encephalopathy with associated sub-clinical epileptiform seizures was made. The patient will remain on anti-epileptic medication and will be regularly reviewed.
in neurology clinic to review his progress. Prognosis for the future is uncertain in this emerging condition.

**Discussion**

We present the case of a 56-year-old male with neuropsychiatric sequelae of COVID-19 encephalopathy including hyperactive delirium associated with confusion, agitation, pressure of speech, formal thought disorder, perseveration and paranoid ideation.

Challenges in this case included the absence of a confirmatory diagnostic test, evolution of the presentation over time and difficulty predicting disease trajectory.

Human coronavirus (hCoV) has neuroinvasive properties and has been suggested to induce overactivation of the autoimmune system in susceptible individuals (Desforges et al. 2014). SARS-CoV-2 may have higher neuroinvasive potential than hCoV predecessors (Natoli et al. 2020). While direct central nervous system pathology due to viral illness is most frequently linked with neurotropic viruses, respiratory viral illnesses (such as the human respiratory syncytial virus (hRSV), the influenza virus (IV), the coronavirus (CoV) and the human metapneumovirus (hMPV)) are also known to be associated with neurological sequelae (Bohmwald et al. 2018). The mechanism of injury causing encephalopathy in COVID-19 patients is likely multifactorial, involving inflammatory, thrombotic, and viral impacts on the endothelium and parenchyma, (Bodro et al. 2020). Although the patient tested negative for COVID-19 during his first admission, sensitivity of nasal swabs is estimated at only 63% (Wang et al. 2020). CT Thorax showing bilateral ground-glass change may be clinically suggestive of COVID-19 (Salehi et al. 2020). It was noted following the Middle East Respiratory Syndrome (MERS) viral pandemic that neurological complications could be delayed 2–3 weeks following respiratory symptoms (Kim et al. 2017). Neurological manifestations of COVID-19 are thought to be both immune and non-immune mediated (Needham et al. 2020), although the pathways are incompletely known at present. Plas mpherasis for COVID-19-related autoimmune meningoen- cephalitis is an emerging treatment which may prove promising (Dogan et al. 2020) and was considered novel at the time of this case. It was unclear in this case what, if any, the contribution of IVIg treatment was to the improvement of the patient.

As a definitive test confirming direct SARS-CoV-2 neuroinvasion was lacking, the patient required extensive investigations, including a brain biopsy, to prove the diagnosis of exclusion. This was a major limitation of this case. While CSF PCR for SARS-CoV-2 is now possible in Ireland, very low positivity rates of PCR for SARS-CoV-2 have been found in COVID-19 patients with acute neurological symptoms (Lewis et al. 2021), although high levels of non-specific autoantibodies in CSF support the argument for an indirect autoimmune response (Lucchese, 2020). This creates a challenge for clinicians treating similar cases, to strike a balance between thorough assessment and over-investigation.

In this patient, an initial EEG at the time of the first neurological presentation was normal, however a later video-EEG showed epileptiform discharges. A case series found that 40% of COVID-19 positive patients had abnormal EEG findings, the most common being frontal sharp wave pattern (Galanopoulou et al. 2020). Frontal sharp wave patterns can indicate interictal epileptiform activity (Kraakow et al. 1999).

Abnormal EEG findings have been shown to be associated with more critically ill patients (Petrescu et al. 2020).

Recovery in this case has been slow but promising, with a protracted period of encephalopathic symptoms. The best predictor of recovery for this and similar patients is likely that of SARS patients. Functional disability in SARS survivors has been found to be due to a complex interplay of physical deconditioning, neuropsychiatric and psychological factors (Hui et al. 2009). Unfortunately, in the COVID-19 cohort, patients admitted with neurological disease have been shown to have higher mortality, higher rates of delirium and greater disability (Benussi et al. 2020). Long term neuropsychiatric, particularly cognitive, complications of COVID-19 are expected to pose future significant challenges to the healthcare system, especially given the high prevalence of the disorder (Needham et al. 2020; Troyer et al. 2020). The new diagnosis of COVID-19 related encephalopathy, although rare, should be included as a differential in patients presenting with new behavioural disturbance, particularly for those in whom COVID-19 is confirmed or suspected.

**Conflict of interest.** Authors have no conflicts of interest to disclose.

**Ethical standards.** The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008. This case report adhered to the standards of the Beaumont Hospital Research and Ethics Committee. Written informed consent was obtained from the patient. Consent was freely and voluntarily given, information regarding the case report was provided in written and verbal form, the patient was given the opportunity to ask questions, with satisfactory answers provided. All data was stored in compliance with the General Data Protection Regulation 2016.

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**References**

Al Saiegh F, Ghosh R, Leibold A, Avery MB, Schmidt RF, Theofanis T, Mouchtoursis N, Philipp L, Peiper SC, Wang Z, Rincon F, Tjoomakaris SI, Jabbour P, Rosenwasser RH, Gooch MR (2020): Status of SARS-CoV-2 in cerebrospinal fluid of patients with COVID-19 and stroke. Journal of Neurology, Neurosurgery, and Psychiatry 91, 846–848 DOI 10.1136/jnnp-2020-332522.

Army Individual Test Battery (1944). Manual of Directions and Scoring. War Department, Adjunct General’s Office: Washington, DC.

Balloy G, Leclair-Visonneau L, Pérén Y, Magot A, Peyre A, Mahé P, Derkinderen P (2020). Non-lesional status epilepticus in a patient with coronavirus disease 2019. Clinical Neurophysiology 131, 2059–2061 DOI 10.1016/j.clinph.2020.05.005.

Benussi A, Pilotto A, Premi E, Libri I, Giunta M, Agosti C, et al. (2020). Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy. Italy Neurology 95, e910–e920 DOI 10.1212/WNL.0000000000009488.

Bernard-Valnet R, Pizzarotti B, Anichini A, Demars Y, Russo E, Schmidhauser M, Ceruttì-Sola J, Rossetti AO, Du Pasquier R (2020). Two patients with acute meningoencephalitis concomitant with SARS-CoV-2 infection. European Journal of Neurology 27, e43–e44 DOI 10.1111/jn.14298.

Bodro M, Compta Y, Sánchez-Valle R (2020). Presentations and mechanisms of CNS disorders related to COVID-19. Neurology(R) Neuroimmunology & Neuroinflammation 8, e23 DOI 10.1212/WNL.0000000000009293.

Bohmwald K, Gálvez N, Ríos M, Kalergis AM, Derkinderen P (2020). Neurologic alterations of CNS disorders related to COVID-19. Neurology 84, 386 DOI 10.1212/WNL.0000000000009848.

Benussi A, Pilotto A, Premi E, Libri I, Giunta M, Agosti C, et al. (2020). Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy. Italy Neurology 95, e910–e920 DOI 10.1212/WNL.0000000000009488.

Bodro M, Compta Y, Sánchez-Valle R (2020). Presentations and mechanisms of CNS disorders related to COVID-19. Neurology(R) Neuroimmunology & Neuroinflammation 8, e23 DOI 10.1212/WNL.0000000000009293.

Bohmwald K, Gálvez N, Ríos M, Kalergis AM (2018). Neurologic alterations due to respiratory virus infections. Frontiers in Cellular Neuroscience 12, 386 DOI 10.3389/fncel.2018.00386.

Desforges M, Le Coupance A, Brison E, Meessen-Pinar M, Talbot PJ (2014). Neuroinvasive and neurotropic human respiratory coronaviruses: potential
neuroviral infections in humans. Advances in Experimental Medicine and Biology 807, 75–96 DOI 10.1007/978-81-322-1777-0_6.

Dogan L, Kaya D, Sarikaya T, Zengin R, Dincer A, Akinci IO, Afsar N (2020). Plasmoderresis treatment in COVID-19-related autoimmune meningoencephalitis: case series. *Brain, Behavior, and Immunity* 87, 155–158 DOI 10.1016/j.bbi.2020.05.022.

Folstein MF, Folstein SE, McHugh PR (1975). “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 12, 189–198 DOI 10.1016/0022-3956(75)90026-6.

Galanopoulou AS, Ferarraauv C, Correa DJ, Cherian K, Duberstein S, Gursky J, et al. (2020). EEG findings in acutely ill patients investigated for SARS-CoV-2/COVID-19: a small case series preliminary report. *Epilepsia* Open 5, 314–324 DOI 10.1002/epi.12399.

Garg RK, Paliwal VK, Gupta A, Galanopoulou AS, Ferastraoaru V, Correa DJ, Cherian K, Duberstein S, Dogan L, Kaya D, Sarikaya T, Zengin R, Dincer A, Akinci IO, Afsar N (2020). EEG findings in acutely ill patients investigated for SARS-CoV-2/COVID-19: a small case series preliminary report. *Epilepsia* Open 5, 314–324 DOI 10.1002/epi.12399.

Garg RK, Paliwal VK, Gupta A (2020). Encephalopathy in patients with COVID-19: a review. *Journal of Medical Virology* 93, 206–222 DOI 10.1002/jmv.26207.

Hsieh S, Schubert S, Hoon C, Mioshi E, Hodges JR (2013). Validation of the Addenbrooke’s Cognitive Examination III in frontotemporal dementia and Alzheimer’s disease. *Dementia and Geriatric Cognitive Disorders* 36, 242–250 DOI 10.1159/000351671.

Huang YH, Jiang D, Huang JT (2020). SARS-CoV-2 detected in cerebrospinal fluid by PCR in a case of COVID-19 encephalitis. *Brain, Behavior, and Immunity* 87, 149 DOI 10.1016/j.bbi.2020.05.012.

Hui DS, Azhar I, Madani E, T. A, Ntoumi F, Kock R, Dar O, Ippolito G, McHugh TD, Memish ZA, Drosten C, Zulma A, Petersen E (2020). The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - the latest 2019 novel coronavirus outbreak in Wuhan, China. *International Journal of Infectious Diseases* 91, 264–266 DOI 10.1016/j.ijid.2020.01.009.

Hui DS, Wong KT, Antonio GE, Tong M, Chan DP, Sung JJ (2020). Coronavirus disease 2019 (COVID-19): a systematic review of imaging findings in 919 patients. *International Journal of Radiology* 215, 87–93 DOI 10.2221/ AJR.2023054.

Irish National Public Health Emergency Team Statement – Saturday 29 February (2020). (https://www.gov.ie/en/press-release/2f75fd-statement-from-the-national-public-health-emergency-team-sat-29-feb/). Accessed 10 July 2020.

Kelly B (2020). Impact of COVID-19 on mental health in Ireland: evidence to date. *Irish Medical Journal* 113, P214.

Kim JE, Heo HJ, Kim HO, Song SH, Park SS, Park TH, Ahn JY, Kim MK, Choi JP (2017). Neurological complications during treatment of middle east respiratory syndrome. *Journal of Clinical Neurophysiology* (Seoul, Korea) 13, 227–233 DOI 10.3988/jcn.2017.13.3.227.

Krakov K, Allen PJ, Symms MR, Fish DR, Lemieux L (1999). Imaging of inter-ictal epileptiform discharges using spike-triggered fMRI. *International Journal of Electroencephalos* 1, 96–101.

Lewis A, Frontera J, Placentonakis DG, Lighter J, Taquet M, Luciano S, Geddes JR, Harrison PJ, et al. (2020). Stereological assessment of hippocampal neuronal loss in patients with COVID-19: a systematic review of imaging findings in 919 patients. *The Lancet Psychiatry* 8, 130–140 DOI 10.1016/S2215-0366(20)30462-4.

Troyer EA, Kohn JN, Hong S (2020). Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. *Brain, Behavior, and Immunity* 87, 34–39 DOI 10.1016/j.bbi.2020.04.027.

Varatharaj A, Thomas N, Ellul MA, Davies N, Pollak TA, Tenorio EL, et al. (2020). Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. *The Lancet Psychiatry* 7, 875–882 DOI 10.1016/S2215-0366(20)30287-X.

Vollono C, Rolle E, Romozzi M, Frisullo G, Servidei S, Borghetti A, Calabresi P (2020). Focal status epilepticus as unique clinical feature of COVID-19: a case report. *Seizure* 78, 109–112 DOI 10.1016/j.seizure.2020.04.009.

Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W (2020). Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA* 323, 1843–1844 DOI 10.1001/jama.2020.3786.

World Health Organization (WHO) (2020, March 11). WHO Director-General’s opening remarks at the media briefing on COVID-19 - 11. Geneva. (https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19--11-march-2020). Accessed 15 July 2020.

Wuhan Municipal Health Commission (2020, January 20). Report of novel coronavirus-infected pneumonia in China. (http://www.wuhan.gov.cn/ front/web/showDetail/2020012009077). Accessed 20 November 2020.