Case report

Non-convulsive status epilepticus: COVID-19 or clozapine induced?

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SUMMARY
We present a case of non-convulsive status epilepticus in a 57-year-old woman with a schizoaffective disorder, without an antecedent seizure history, with two possible aetiologies including SARS-CoV-2 infection and clozapine up titration. We discuss the presentation, investigations, differential diagnosis and management. In particular, we focus on the electroencephalogram (EEG) findings seen in this case and the electroclinical response to antiepileptic medication. We review the literature and discuss the relevance of considering possible neurological manifestations of SARS-CoV-2 infection and highlight seizure disorder as one of the possible presentations. In addition, we discuss the possible effects of clozapine on the electroclinical presentation by way of possible seizure induction as well as discuss the possible EEG changes and we highlight that this needs to be kept in mind especially during rapid titration.

BACKGROUND
The COVID-19 pandemic has had an unprecedented impact on global health. We illustrate one of the less reported possible manifestations of the SARS-CoV-2 infection in order to bring further awareness to one of the probable neurological implications of this infection. We describe a case of non-convulsive status epilepticus (NCSE) in a 57-year-old woman, without an antecedent seizure history. We highlight seizure disorders as a possible manifestation of SARS-CoV-2 infection and describe the complexity of these presentations in the intensive care setting, especially in the context of atypical antipsychotics such as Clozapine.

CASE PRESENTATION
A 57-year-old right-handed woman presented with shortness of breath and fever in mid April 2020. The patient was lethargic and too breathless to provide a history of the events leading up to admission. A collateral history was taken from her sister who explained that she had become non-verbal in the week prior to admission and had been increasingly breathless. For the previous 18 months she had resided in a mental health hospital being treated for schizoaffective disorder. Her medical history includes depression, pancreatectomy, splenectomy (for which she is on long-term antibiotics), and chronic obstructive pulmonary disease. She has a long smoking history (40 pack/year). Prior to admission, she had a good exercise tolerance and despite having inhalers, rarely used them. She had a pulmonary embolism in October 2019, which was provoked after a traumatic fall sustaining multiple fractures. She had type 2 diabetes mellitus, which was managed with metformin and insulin. She had also reported episodes of mutism and unresponsiveness (lasting several days at a time). These events were considered to be related to her mental health disease.

On examination at presentation, she was saturating at 91% on 40% oxygen and was unable to speak due to breathlessness. Her respiratory rate was 22 breaths per minute and she was hypotensive. An arterial blood gas indicated a type 1 respiratory failure (PaO2 7.2 kPa and PaCO2 4.0 kPa). Her Glasgow Coma Score (GCS) was seven (without pain and opening eyes to pain, without a verbal response). She was transferred to intensive care for intubation and ventilation the day after admission. She was treated with antibiotics to cover a community-acquired pneumonia and treated for an Epstein-Barr viraemia. She was nursed prone for acute respiratory distress syndrome. She developed an acute kidney injury for which she required haemofiltration. She was intubated and ventilated for one month. Her sedation was gradually lightened as she was weaned off the ventilator. Her GCS was 15 by the 25th of May and she was self-ventilating. She was weak in all four limbs. Two days later she was less engaged, she was unable to speak or obey commands and opened her eyes only to pain. Some new onset intermittent right-sided facial jerks were noted. She was diagnosed with NCSE on electroencephalogram (EEG). She was commenced on Levetiracetam. During the next 12 hours, her GCS improved to 14, she was opening her eyes spontaneously, and obeyed motor commands; however, was not completely oriented to time or place and a repeat EEG confirmed a resolution of the status epilepticus (figure 1).

INVESTIGATIONS
She underwent several investigations during her admission. Nasopharyngeal and oropharyngeal swab specimens were obtained and real-time PCR (RT-PCR) assay was performed, which tested positive for SARS-CoV-2. She had a CT brain scan without contrast which demonstrated bilateral calcification of the globus pallidus in keeping with mild age-related changes. An MRI brain scan was normal. These two scans were done when the
Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

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Figure 1  (A) Electroencephalogram (EEG) findings in keeping with non-convulsive status epilepticus with clear electroclinical improvement after lorazepam administration. (B) EEG after treatment with antiepileptic medication one day later showing frequent multifocal epileptiform discharges as well as intermittent frontotemporal theta/delta waves.

patient was noted not to be waking following extubation, first as she was quadriplegic at this time and second to consider if there were any MRI features known to be associated with COVID-19. At day ten postextubation, she underwent an EEG. Frequent (2.5–4 Hz), florid bilateral, non-synchronous epileptiform discharges were seen over both hemispheres throughout most of the recording. The patient was unresponsive during this period of recording. 2mg of intravenous lorazepam was given, after which the epileptiform discharges subsided and a 6–7 Hz background predominated. The patient became slightly more alert, in that she could obey some motor commands and vocalise to a small extent. The EEG findings were in keeping with NCSE with clear electroclinical improvement after lorazepam administration (figure 1A). One day later, she had another EEG study to investigate whether there were residual subclinical seizures. The EEG showed a background rhythm reaching 7–8 Hz, which was reactive to external stimulation. Frequent multifocal epileptiform discharges were seen as well as intermittent frontotemporal theta/delta waves. There was a significant improvement compared with the first EEG study. There was no evidence to suggest NCSE; however, frequent epileptiform discharges were seen over both hemispheres, without a clear focus (figure 1B).

DIFFERENTIAL DIAGNOSIS
We consider whether the NCSE was indeed precipitated by SARS-CoV-2 infection, or whether it may have been clozapine induced.

TREATMENT
After being diagnosed with NCSE, the patient was initially loaded on Levetiracetam and then continued on 500 mg twice daily. During her admission, her regular Clozapine dose of 150 mg in the morning and 300 mg at night was held. This was gradually reintroduced by psychiatry in increments during the first six weeks of her stay. At the time of onset of her facial jerks and lower GCS, she was taking 100 mg in the morning and 175 mg at night. This was then reduced abruptly the following day to 125 mg at night only, and the following day, when the EEG confirmed NCSE, she was prescribed clozapine 50 mg two times per day (figure 2).

OUTCOME AND FOLLOW-UP
The patient gradually improved in that she was able to verbalise and obey motor commands. She still however had episodes of fluctuating confusion three weeks after being discharged to the neurology ward; however, she did have a concomitant urinary tract infection at that time.

DISCUSSION
COVID-19 is of critical concern worldwide not only for its rapid transmission but also for its relatively heterogeneous presentation. The coronaviruses including SARS-CoV-2 have been reported to have neuroinvasive properties. SARS-CoV-2 is thought to be able to access cells that display the angiotensin-converting enzyme 2 (ACE-2), which is expressed on both glial cells and neurons. Various neurological presentations have been linked to SARS-CoV-2, including encephalitis. We describe a SARS-CoV-2 positive case presenting with NCSE and discuss the possible aetiologies.

In terms of our patient’s psychiatric history, her schizoaffective disorder had been stable for the past few years following the introduction of Clozapine. Clozapine is an atypical antipsychotic, widely used for its superior efficacy in the management of treatment-resistant schizophrenia and schizoaffective disorder. Its superior efficacy over other antipsychotics has been confirmed by multiple studies and it is therefore widely used despite its numerous side effects. Our patient’s Clozapine was stopped on admission and then uptitrated, and reduced quickly when she was found to be in NCSE (figure 2). Clozapine can interact with general anaesthetics potentiating central nervous
system depression and a subsequent slow emergence from anaesthesia. This may be one contributor to our patient’s variable recovery post extubation. A notable adverse effect of Clozapine is precipitation of seizures, which have been observed at all stages of Clozapine treatment, hence the reason why her Clozapine was weaned rapidly over five days at the time that the patient dropped her GCs and presented with facial jerks. At the time of detection of NCSE on EEG, her dose was 50 mg twice daily and she was not toxic (figure 2). Seizures have been observed at low doses during the titration phase and at high doses during the maintenance phase of Clozapine.2,4,6

As many as eight percent of patients taking Clozapine have focal or generalised seizures; however, there is no robust evidence for Clozapine-induced NCSE currently in the literature. The average time to develop seizures after Clozapine initiation is reportedly between 34 and 42 days.7 It is important to note that Clozapine can impact the EEG. Varma et al.8 described that of 565 patients on Clozapine, 347 had an abnormal EEG. There is no clear evidence describing the effects of intravenous Lorazepam on Clozapine-induced epileptiform discharges. However, as we generally consider these discharges to be interictal, we do not predict benzodiazepines to have a modifying effect on them, rather we would expect an abundance of fast activity.

Several reports have been published associating SARS-CoV-2 with new onset seizures. Six early case reports from the COVID-19 pandemic have reported seizures as a manifestation of the infection. These accounts range from single generalised tonic-clonic (GTCS) seizures,9,10 multiple GTCS, multiple focal seizures and one case of status epilepticus, described as ongoing myoclonic activity of the right face and limbs.9,12 The average age of the patients was 49 years (range 24–78 years). Two cases were from the USA, and other reports came from Italy, Iran, Japan and Germany. In five out of the six patients, there was no prior history of seizures or a family history of epilepsy. All initially developed symptoms of SARS-CoV-2 (including fever, dry cough, fatigue, myalgia) and subsequently had seizures during their clinical course. All six tests positive for COVID-19, but only two patients had cerebrospinal fluid (CSF) PCR tested for SARS-CoV-2, one being positive. The MRI in this patient displayed the radiological features of encephalitis.13

Our patient’s EEG pattern is in keeping with the Salzburg criteria for NCSE in that the epileptiform discharges were at a frequency of ≤2.5/5 and there was electroclinical improvement with application of intravenous benzodiazepine. We conclude that the two most likely aetiologies for her NCSE include either SARS-CoV-2 infection and/or the reintroduction and relatively rapid up titration of Clozapine. The patient did not undergo a lumbar puncture however as she was clinically improving with antiepileptic treatment and this investigation could not be clinically justified. We could not therefore demonstrate the presence of SARS-CoV-2 in the CSF. We hypothesise that SARS-CoV-2 could trigger seizures through a neurotropic pathogenic mechanism and subsequently emphasise the importance of considering possible neurological manifestations, including seizure disorder of SARS-CoV-2 infection. In addition, atypical antipsychotics such as Clozapine can induce both seizures and EEG changes and this needs to be kept in mind especially during rapid titration in the intensive care unit (ITU) setting.

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