COVID-19 Encephalopathy in the Context of Psychiatric Comorbidity: Case Report and Diagnostic Pitfalls

David Benrimoh, MD.CM., MSc.

Department of Psychiatry, McGill University

Vincent Jetté Pomerleau, M.D. M. Sc.

Department of Psychiatry

McGill University

vincent.jettepomerleau@mail.mcgill.ca

Thank you David

Majed A. Alharbi M.D

Department of Psychiatry

McGill University

majed.alharbi@mail.mcgill.ca

Department of Psychiatry

King Abdulaziz Medical City,

Riyadh, Saudi Arabia.

Louis Pinard M.D., FRCPC

Department of Psychiatry

MUHC

Assistant Professor

Department of Psychiatry

McGill University

Leon Tourian, MSc, MD, FRCP

Department of psychiatry

MUHC

Associate professor

McGill University

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Abstract:

We present the case of likely COVID-19 associated encephalopathy in a male in his early 50s with a history of non-psychotic depression and personality disorder who presented with delirium, new psychotic symptoms and who developed paratonia and obtundation. After initial questions of neuroleptic malignant syndrome, serotonin syndrome, and stiff person syndrome were decided to not be supported by the clinical picture, conservative management and the repeated treatment of a co-occurring mastoiditis led to improvement of mental status, regained ability to walk and speak, though a dysexecutive syndrome was left when patient was discharged to rehabilitation services. We explore the role the patient's psychiatric comorbidity had in terms of both his clinical course and the decisions and diagnostic considerations of the various treating teams involved.

Introduction:

COVID-19 has now been established as a viral infection with various possible neuropsychiatric manifestations (Ellul et al., 2020). This may present a challenge when attempting to provide an appropriate diagnosis of altered mental status (AMS) when treating patients with both COVID-19 and pre-existing psychiatric comorbidity, as there may be risk of inappropriate or erroneous treatments or investigations if the AMS is too readily ascribed to either the COVID-19 infection or to the psychiatric condition. Here, we report the case of a patient with COVID-19 infection, encephalopathy and psychiatric comorbidity, and discuss the lessons his clinical course may impact on the importance of carefully separating psychiatric and non-psychiatric causes of AMS in the context of an individual patient, as well as on the importance of clear communication and thoughtful clinical decision-making, even in the context of a global pandemic.

Setting for the case and sources of information:

This patient's clinical course stretched across two hospitals in the Montreal area between early June and late September 2020. As will be discussed, he was initially admitted to a community hospital prior to being transferred to a tertiary center, where the authors of this report were involved in his care as part of the consult-liaison psychiatric team. Information on the case was gleaned from the written medical records transferred from the community hospital, brief discussions prior to patient transfer with physicians at the community hospital, the patient's chart at the tertiary care center (which included his previous psychiatric follow-up), and the authors' interactions with the patient and his family. The lack of a unified medical record, however, did make extracting some details challenging during this case.

Prior to the patient's discharge, the possibility of his case being appropriate material for a case report was discussed with him and he provided verbal consent for the authors to publish and

was documented in the medical chart. Names and certain medically irrelevant details have been changed to ensure the confidentiality of the patient and his family.

The case of Mr. P:

Mr. P is a married male in his early 50's. He was working in maintenance prior to his contracting of COVID-19. He had had a recent impulsive suicide attempt which predated the hospitalization in question in this report by several months. He is known for hypertension, bilateral knee osteoarthritis, and is a smoker. He previously had an alcohol and polysubstance use disorder, but had been abstaining from alcohol for nearly a decade and from other drugs for over three decades. He is followed by a psychiatrist and known for ADHD, a mixed personality disorder with elements of borderline and dependent personality, and recurrent major depressive episodes. He has also been followed in couple therapy and has a past history of traumatic experience. His outpatient medications included citalopram 40 mg, methylphenidate 5 mg BID, quetiapine extended-release 400 mg qhs, as well as ramipril, atorvastatin, hydrochlorothiazide, amlodipine, metoprolol, and vitamin D supplementation.

Mr. P was in his usual state of health, including complete independence of all activities and instrumental activities of daily living as well as normal cognitive function, until early June 2020 when he was admitted to the intensive care unit of his community hospital for COVID-19 pneumonia. He required supplemental oxygen and became agitated and delirious. He began to experience delusions and auditory and visual hallucinations, which were not and, according to his medical records, had never been part of his usual psychiatric presentation. These hallucinations and delusions included him coming to believe he had locked a woman in the bathroom, and then putting his hand through a glass panel, causing his wrist to bleed. At the time he was seen by the consultant psychiatrist at the hospital, who stopped his methylphenidate and citalopram. After two negative COVID-19 tests, and while he- by reports of his family- was still in an acutely delirious state, he was discharged home, apparently with his outpatient psychiatrist as the primary clinician involved who could provide further treatment of his altered mental status. Within 24 hours of discharge, his family brought him to the emergency room of the tertiary care center as they did not feel he was safe at home and he was experiencing hallucinations and behavioral disorganization which were not his familiar psychiatric symptoms; he was transferred back to the community hospital for continuity of care.

When he returned to the community hospital he was found to be febrile, up to 42 degrees Celsius. He was given antibiotics and all of his psychiatric medications were stopped at this point. Based on the high temperature and reported muscle rigidity, a presumptive diagnosis of neuroleptic malignant syndrome versus serotonin syndrome was made. Stiff person syndrome was also in the differential diagnosis. There is mention in notes in the chart sent from the community hospital of a creatine kinase (CKs) in the 3000's, though this seems isolated and the rest of the values on record were in the 200-300 range prior to normalization. In terms of serotonergic load, the patient had had his antidepressant stopped days before; in terms of antipsychotics, he had only received his usual quetiapine, which he had been stable on at the same dose for 3-4 months (he had been on quetiapine previously as well, but at a lower dose).

He was agitated, and was treated for this using diazepam, ketamine, and dexmedetomidine. The patient was also intubated at this point. Note that an MRI of his brain at the community hospital demonstrated no acute abnormalities, though a bilateral mastoiditis was noted.

He eventually stabilized and was able to be extubated. He was then transferred to the ICU at the tertiary hospital as he had persistent altered mental status of unclear cause, the agitation was difficult to manage, and there were no readily available psychiatric or neurological services available at the community hospital. These services were necessary to clarify the diagnosis responsible for the persistent altered mental status and changes in muscle tone. At the tertiary hospital, consultations for both neurology and consult-liaison psychiatry were requested. Both teams examined the patient in the ICU, on and off of propofol sedation, and came to the same conclusion that, at least at that point, no rigidity could be objectified on exam. Rather the patient was sometimes supple in tone, and at other times significantly paratonic, at times actively resisting extension of his limbs and digits and appearing to be in pain. He appeared to have painful contractures, potentially related to his extended ICU stay. He also appeared to have a new drop foot on the left, which was either a result of systemic inflammation or ICU-related nerve compression.

While the physical examination and CK values at the time of admission to the ICU at the tertiary hospital were not in keeping with the diagnosis of NMS or serotonin syndrome, the patient was nevertheless given a full course of bromocriptine, dantrolene, and diazepam. Antipsychotics were also avoided. These did not improve his mental status or his paratonia, though the diazepam was effective in reducing agitation. He was also given valproic acid and mirtazapine to help control his agitation. He continued to spike fevers despite a course of piperacillin-tazobactam and meropenem in the ICU, and his mental status remained concerning. He was essentially fully obtunded, replying only at times to his name by looking in the general direction of the speaker; he was unable to track movement; he was nonverbal; and he was constantly moving his legs when not sedated, likely in a delirious attempt to leave the bed or to get more comfortable, though the movements seemed almost choreic at times. He was, on the advice of neurology, intubated again and sent for a repeat MRI brain. This resulted in another scan with no acute features other than a persistent bilateral mastoiditis. He also had a lumbar puncture and workup for antibodies (such as anti-NMDA) and paraneoplastic markers; all were non-contributory. Regrettably, CSF COVID-19 antibody screen or viral load were not done.

A pivotal discussion then occurred between neurology and consultation-liaison psychiatry regarding diagnosis and plan. It was agreed that the physical and mental examination did not support a diagnosis of neuroleptic malignant syndrome or of serotonin syndrome. In addition, it was agreed that the MRI and LP results did not support an encephalitis diagnosis. Finally, it was agreed that a primary psychiatric diagnosis, such as catatonia, was not likely and as such there was likely little benefit to attempting electroconvulsive therapy. The presumptive diagnosis became a COVID-19 encephalopathy, and, given the lack of knowledge about how to treat this condition, the decision was made to provide supportive care and to observe the patient's course. Mirtazapine and diazepam primarily were used to manage anxiety. The patient had

some small reduction in agitation and his vital signs stabilized sufficiently that he was transferred to the internal medicine ward.

Internal medicine then made the decision, given the persistent fever spikes and redemonstration of mastoiditis on MRI, to try another course of piperacillin-tazobactam and meropenem. Within 24 hours the patient was no longer febrile, and over the next few weeks, his mental status finally began to improve. His speech returned, though he was still delirious and had poor attention and orientation. Over the space of days, his attention as measured by digit span improved, and he became less and less delirious. Physically, he still had painful contractures and poor coordination which required OT and PT support to help him improve his function. He was eventually able to begin feeding himself and to progressively regain function in his hands and the ability to walk with assistance.

Prior to discharge, Mr. P was able to enjoy visits from his family and to have normal conversations with psychiatric staff. He seemed to still have difficulty with sustained attention (such as serial 7's) and he began to experience what appeared to be frontal affect. This, in combination with a positive palmomental reflex, supported the presence of a dysexecutive syndrome, which has previously been described in cases of COVID-19 (Helms et al., 2020). The patient's mirtazapine was increased slowly, resulting in improved sleep and some improvement in affect prior to his discharge to a convalescence center. Final diagnosis as per internal medicine was of a delirium related to infection, and as per neurology was of a COVID-19 related encephalopathy, due to the absence of any other compelling cause. Psychiatry had the opinion that this was in fact a COVID-19 related encephalopathy, given the dysexecutive syndrome the patient was left with at discharge and delirium stretching back to the initial infection, with a bacterial superinfection which prolonged the altered mental status.

DISCUSSION

The case of Mr. P and his remarkable recovery is one that has lessons to teach us in the context of the current pandemic. It is worth first briefly reviewing COVID-19 related encephalopathy. An excellent recent review article (Ellul et al., 2020) provides us with varying prevalence rates for encephalopathy- from 7% in a study of 214 hospitalized patients from a sample in Wuhan, China (Mao et al., 2020), to 13% in a national registry sample of 125 patients in the U.K. (Varatharaj et al., 2020), to 69% of 58 ICU patients in a French study (Helms et al., 2020). . The overall impression, however, is that this virus has frequent neuropsychiatric manifestations, and that these may include encephalopathy, as well as a dysexecutive syndrome (Helms et al., 2020). Many, but not all, patients with neurological manifestations of COVID-19 have MRI findings (Kremer et al., 2020; Katal et al., 2020). Several hypotheses account for the entry of this virus into the central nervous system; one is that the virus directly infects the brain through the olfactory bulb, and another posits hematogenous entry via the blood brain barrier; both may contribute to the observed symptoms of COVID-19 neurological infection (Kumar et al., 2020). With respect to the mechanism of disturbance of neurological function, both the immune response to the virus and a direct cytopathic effect have been postulated (Kumar et al., 2020).

Perhaps the most interesting point in the context of Mr. P's psychiatric comorbidity is in fact *how little* his psychiatric conditions actually had to do with his presentation, while at the same time *how much* these comorbidities seemed to influence decision making at critical junctures. For example, it remains unclear why a patient with clear delirium- symptoms not at all in keeping with his usual psychiatric symptoms- would be discharged home, with the expectation that outpatient psychiatric management would be of use in treating his still acute condition. Following this, the diagnosis of NMS or serotonin syndrome (versus stiff person syndrome) seems in retrospect to have been hasty considering these are diagnoses of exclusion and the patient's actual exposure to the usual culprit medications was minimal. Instead, he had a cause for fever (the mastoiditis) and the rigidity seems rather to have been a paratonia better explained by a mixture of painful contractures, extended ICU stay, and delirium. Even his sad affect noted once his mental status improved seemed rather to be a case of frontal affect than his usual major depression. Finally, the diagnosis of NMS and possible catatonia persisted- despite the fact that psychiatry stopped using these diagnoses and clearly wrote encephalopathy in every progress note- potentially taking the focus off of other contributory conditions, such as the mastoiditis. One might question whether the persistent focus on psychiatric comorbidity may have delayed the identification and treatment of other disorders- such as the mastoiditis- or the consideration of COVID-19 as a primary contributing cause. Conversely, the power of effective and transparent communication was demonstrated when the discussion between psychiatry and neurology led to the decision to offer supportive treatment rather than invasive intervention, which ultimately allowed Mr. P, after the second course of mastoiditis treatment, to recover and improve without the potentially significant side effects of immune-suppressant therapies which had been considered as treatments for a presumptive encephalitis, or of ECT for some variant of catatonia.

The clinical pearls that can be drawn from this case are therefore as follows:

1. Altered mental status, when acute, should be considered a medical problem until proven otherwise, in order to ensure appropriate consideration of common and potentially dangerous diagnoses
2. The assessment of altered mental status in a psychiatric patient should occur in context of their known symptomatology; it is not appropriate to assume hallucinations or delusions, for example, are of psychiatric origin in cases where these would be new symptoms for a given patient. This in turn highlights the importance of ensuring adequate information transfer between sites and healthcare systems, and of communication between clinicians
3. COVID-19 has a wide range of possible neuropsychiatric manifestations, which may be both acute (i.e. AMS) and chronic (potentially dysexecutive syndrome) in nature, and which require treatment by a multidisciplinary team that communicates well, and ideally with the involvement of family so that new symptoms (i.e. affective dysregulation) can be differentiated from previous symptomatology in those with pre-existing psychiatric disorders

4. Conservative treatment, including reconsideration of previously treated illnesses (in this case, the mastoiditis), and observation, remain powerful clinical tools when the diagnosis or effective treatment plans remain unclear

Mr. P also benefited significantly from the advocacy of his family members. In the current climate- when many patients' families are not able to come to the hospital because of visiting restrictions- it is key for clinicians to remember to engage families in order to help clarify patient symptoms and previous baseline functioning.

The case of Mr. P was a diagnostic challenge, one made more complex by psychiatric comorbidity which, ultimately, was not an important part of his presentation, being significantly overshadowed by his COVID-19 encephalopathy and his delirium-prolonging mastoiditis. The emphasis placed on his psychiatric history early in the course of his illness, and the potential dangers in terms of early discharge while delirious and diagnostic confusion this caused, serves as a cautionary tale for clinicians assessing AMS in COVID-19 patients with previous psychiatric history.

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