Covid-19, Neuroleptic Malignant Syndrome and Psychosis

Dr Calum Grant [1] Dr Jonathan A Keay [2] Dr Bardhan Jung Shah [3] Dr Babatunde Adeeko [3]

[1]FY1 Doctor; Queen's Hospital; Barking, Havering and Red-bridge University Hospitals NHS Trust [2]Fellow in Medical Education; North East London NHS Foundation Trust [3]Consultant Psychiatrist; Goodmayes Hospital; North East London NHS Foundation Trust

Introduction

Neuroleptic malignant syndrome (NMS) can be a severe condition; misdiagnosis or delay in initiating treatment can prove fatal. An unusual presentation of NMS is outlined here in a patient being restarted on Clozapine following a mild COVID-19 infection.

NMS, for which the diagnostic criteria are outlined below, typically arises through an idiosyncratic drug reaction to medications with dopamine receptor-antagonist properties, or in cases of rapid withdrawal of dopaminergic medications which precipitate the dysregulation of various central neurochemical and neuroendocrine systems.

DSM-5 criteria for diagnosing NMS

Include having the three major criteria of:

- Exposure to a dopamine antagonist
- Muscle rigidity
- Hyperthermia

Additionally, at least two minor criteria must be present, from: tachycardia, tremor, altered level of consciousness, labile blood pressure, diaphoresis, leucocytosis, and elevated Creatine Kinase (CK).

Patient Background

The patient was a 56-year-old white male who was living alone with support from family in the area. He had longstanding treatment resistant schizophrenia for which he was treated with clozapine. He had been stable in the community for almost two decades.

His past medical history included type II Diabetes, hypercholesterolemia and Iron deficiency anaemia. Medications on admission included: Aripiprazole 10mg once daily, Venlafaxine 150mg twice daily.

The Case

The patient was engaging with clozapine blood monitoring services every 4 weeks. One such appointment returned an amber result, meaning the neutrophil levels were borderline; while he could continue taking clozapine the frequency of blood monitoring had to be increased.

Before the next blood sample the patient developed flu like symptoms and subsequently tested positive for Sars-Cov-2. He was forced to self-isolate for 10 days, thereby missing the appointment. This resulted in clozapine treatment being abruptly discontinued. Following a five-day gap in which no antipsychotic was prescribed Aripiprazole 10mg was started in the community, with a view to re-titrating clozapine after 2 green results could be returned from monitoring services.

His COVID-19 infection was mild and did not require hospitalisation. When family observed the patient immediately following his isolation period they became extremely concerned regarding his mental state. He was taken to an emergency department presenting with pressured speech, confusion and violent paranoid thoughts.

On being medically liaison psychiatry services organised transfer to a psychiatric ward as an informal patient. The impression on admission was that of a psychotic relapse, likely due to clozapine discontinuation. The plan was to retitrate clozapine.

Table 1:Blood results

Test	Result	Reference Range
Hb	126	133 - 173 g/L
WBC	17.7	3.8 - 11x10*9/L
Urea	21.5	2.5 - 7.8 mmol/L
Creatinine	149	59 - 104 umol/L
CRP	28	0 - 5 mg/L
Troponin T	38	0 - 13 ng/L

Management

After taking two 12.5mg doses of clozapine 12 hours apart the patient was reported by nursing staff as having difficulty mobilising, being incontinent of urine, and confused. It was now 2 weeks since the patient tested +ve for Sars-Cov-2, and over 1 week since completing his isolation period.

On review the patient presented with pressure of speech. No rigidity was found clinically; patient was afebrile and tachycardic (145/min). ECG showed sinus tachycardia with QTc within normal limits. Bloods were requested (Table 1), patient was unable to cooperate to provide a sample for urinanalysis.

The impression was Acute Kidney Injury (AKI) secondary to urinary tract infection (UTI). The confusion was speculated to be due to possible delirium. The patient was transferred to an acute medical ward for treatment. Here the patient's Creatine Kinase (CK) was found to be grossly elevated at approximately 32 000 IU/L (Table 2).

Computed tomography pulmonary angiogram (CTPA) ruled out Pulmonary embolism (PE). Head computed tomography (CT) was unremarkable. He tested positive for Sars-Cov-2, though this was likely residual viral Ribonucleic acid (RNA) from his previous infection.

He was treated over the course of several days for NMS, UTI, AKI and COVID-19 with fluids, antibiotics, and supportive therapies. All anti-psychotic agents were discontinued.

Table 2:Hospital Admission Blood results

Test	Result	Reference Range
D-dimers (Innovance)	2.16	0 - 0.5 mg/L FEU
Creatine Kinase (CK)	32321	40 - 320 iu/L
Amylase	204	0 - 100 iu/L
C-Reactive Protein	63	0 - 5 mg/L

Further Investigation

On being medically cleared several days later the patient returned to the psychiatric ward. His urea and electrolytes returned to normal limits, but the tachycardia remained. Echocardiogram, 24-hour electrocardiogram, and deep vein thrombosis clinic found no medical explanation for the tachycardia, which was subsequently treated with Bisporolol on the advice of cardiology. Clozapine was then able to be restarted without further NMS complications.

Conclusion

The presentation reported here only met one of the three major DSM-5 diagnosing criteria for NMS - exposure to a dopamine antagonist. He met several minor criteria, including altered levels of consciousness, elevated CK, tachycardia, and urinary incontinence.

Various aspects of the case, however, are out of keeping with previously reported NMS findings.

Firstly, there was an absence of relatively fast titration schedules or rapid dose increases of anti-psychotic agents. The patient had only received two small doses of clozapine, combined with two weeks of Aripiprazole.

Secondly, while the lack of fever is in keeping with the second generation anti-psychotic drug therapy combination, the grossly elevated CK is highly unusual. The AKI secondary to the UTI likely contributed to raised CK levels but is insufficient to explain the degree of elevation.

The extent to which prior COVID-19 infection played a role in this case remains unclear.