Neuroleptic malignant syndrome following reintroduction of an antipsychotic after overdose

Théo Korchia,1,2 Graham Blackman,2 Michel Cermolacce,1 Raphaëlle Richieri1,2,3

SUMMARY
Neuroleptic malignant syndrome (NMS) is a potentially lethal adverse drug reaction. We report a case of NMS potentially induced by dehydration in a female patient suffering from schizoaffective disorder. We discuss possible aetiologies and triggering factors alongside the existing literature.

BACKGROUND
Neuroleptic malignant syndrome (NMS) is a potentially lethal adverse drug reaction that affects 0.2% to 3.2% of psychiatric inpatients.1 Despite being a well-recognised condition, the pathogenesis of NMS is not fully understood. Although many risk factors have been identified, predicting which patients will develop NMS and when, remains extremely difficult.2 We report a case of NMS and discuss possible aetiologies with reference to the existing literature.

CASE PRESENTATION
A 57-year-old woman with an established diagnosis of schizoaffective disorder was admitted to the emergency department following an attempted suicide by taking an overdose of cyamemazine 750 mg (a first-generation antipsychotic of the phenothiazine class) and lercanidipine 300 mg (an antihypertensive of the dihydropyridine class of calcium channel blockers) tablets.

She had a medical history of obesity (body mass index 33 kg/m²), obstructive sleep apnoea, cholecystectomy, well-controlled hypertension, type 2 diabetes and hyperlipidaemia and was prescribed bisoprolol, lecanidipine, atorvastatin and metformin. For management of her schizoaffective symptoms, she was prescribed zuclopenthixol decanoate 300 mg monthly (a long-acting injectable antipsychotic) and cyamemazine 50 mg daily.

She was asymptomatic on arrival to the emergency department, however subsequently developed vasoplastic syndrome requiring admission to intensive care unit (ICU) and treatment with intravenous norepinephrine 4 mg/hour for hypotension. After a 3-day medical admission, she was transferred to a psychiatric ward.

OUTCOME AND FOLLOW-UP
A clinical diagnosis of NMS was made. All antipsychotics were discontinued, and she spent a 10-day period on ICU where she received rehydration therapy, muscle relaxants and regular benzodiazepines (oxazepam 30 mg daily) leading to full resolution of her neurological symptoms and confusion. After being transferred back to a psychiatry ward, she was not restarted on antipsychotic medication but was instead treated with a course of electroconvulsive therapy. This led to a significant improvement in her psychotic symptoms by the third session.
(20 days after the onset of NMS). At follow-up, 11 months after the onset of NMS, she remained neurologically intact and her schizaffective symptoms remained partially controlled on maintenance electroconvulsive therapy (ECT) without antipsychotic medication.

DISCUSSION

We describe a case of NMS occurring in a patient with schizaffective disorder after receiving excessive amounts of antipsychotic medication on two occasions within a 6-week period: the first in the context of an attempted suicide and the second following an accidental overdose due to an administration error. According to Diagnostic and Statistical Manual of Mental Disorders (DSM-5), diagnosis of NMS requires a patient to meet the following major criteria: (1) exposure to a dopamine blocking agent, (2) severe muscle rigidity and (3) fever, and at least 2 of 10 minor criteria.8 Our patient presented all of the major criteria, and seven of the minor criteria (raised CK, diaphoresis, tachycardia, increased blood pressure and heart rate, altered consciousness and leucocytosis). While the patient clearly displayed the classic features indicative of NMS, there are several atypical aspects of the case worthy of discussion.

Notably, the patient did not develop NMS until 2 months after the iatrogenic overdose of zuclopenthixol. This is surprising given that maximum serum concentration following intramuscular injection of zuclopenthixol acetate occurs after 24–48 hours, and plasma elimination half life is approximately 20 hours.9 Further, around the time of the medication error, additional risk factors for NMS were present, including concomitant treatment with two first-generation antipsychotics and psychomotor agitation.1 5 Instead, NMS occurred later while being prescribed a single antipsychotic (zuclopenthixol dihydrochloride) at a low dose.

In the present case, acute renal failure (ARF) and hepatic cytolyis were not the sequela of NMS. Rather, they predated NMS, and therefore may have played a causative role2 6 by impairing the metabolism and excretion of zuclopenthixol leading to elevated serum concentrations of the drug. Also of note, escitalopram, which is a cytochrome P450 2D6 enzyme inhibitor, was prescribed at the time NMS developed, and therefore may have contributed towards raised serum concentrations of zuclopenthixol.

The pathogenesis of NMS can be considered a complex cascade of dysregulation of multiple neurochemical and neuro-endocrine systems, culminating in an end-stage hypermetabolic syndrome.7 A central dopaminergic blockade theory has been proposed to explain NMS involving striatal and hypothalamic dopamine receptors.8 There is also evidence to suggest that dysregulation of the sympathetic nervous system may account for, at least some of, the features of NMS.3 Finally, more recently a neuroimmunological explanation of NMS has been proposed, implicating the role of proinflammatory cytokines.10 In our case report, the elevation of fibrinogen (an acute phase protein) is consistent with this later hypothesis, with the patient’s dehydration potentially acting as an inflammatory stimulus.

This case report highlights the importance of recognising that patients may develop NMS several years after starting antipsychotic therapy. Furthermore, NMS may occur any time, but particularly in the presence of additional risk factors, such as dehydration. ARF in the presence NMS is associated with a mortality risk of approximately 50%,11 therefore, it is vital that clinicians are vigilant for evidence of dehydration in patients treated with antipsychotics.

REFERENCES

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Patient’s perspective

The ECT allowed me to resume activities that I had not been doing for several years as dancing, seeing friends, playing cards and improved substantially my quality of life.

Learning points

► Neuroleptic malignant syndrome (NMS) is a serious and potentially lethal adverse drug reaction.
► NMS is unpredictable but is related to the administration of dopamine antagonists.
► NMS can be best described as a complex cascade of multiple dysregulated neurochemical and neuroendocrine systems, potentially culminating in an end-stage hypermetabolic syndrome.
► Risk factors for NMS, such as dehydration as well as renal and hepatic impairment, should be considered prior to, and during treatment with antipsychotics.

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Contributors

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Unexpected outcome (positive or negative) including adverse drug reactions