Med & Health Jul 2025; 20(2): 829-834 https://doi.org/10.17576/MH.2025.2002.35

CASE REPORT

Understanding Neuroleptic Malignant Syndrome: Lessons from a Near-Miss Case

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Received: 08 September 2024 / Accepted: 09 October 2024

ABSTRAK

Sindrom neuroleptik malignan (NMS) adalah suatu keadaan yang jarang berlaku dan boleh membawa maut. Komplikasi yang tidak diingini boleh dielakkan dengan pengesanan awal dan pemberhentian ubat yang menjadi punca, diikuti dengan rawatan agresif. Kami melaporkan kes seorang lelaki muda yang menghidap skizofrenia, yang mengalami perubahan keadaan mental dan hipertermia selepas diperkenalkan dengan olanzapine. Beliau menghidap NMS yang turut menyebabkan rabdomiolisis dan kecederaan buah pinggang akut. Walaupun pesakit menunjukkan beberapa tanda yang mencadangkan NMS, diagnosis tidak dibuat dengan segera, menyebabkan kelewatan dalam rawatan. Keadaan ini mungkin disebabkan oleh jarangnya kejadian NMS berlaku, persamaan gejalanya dengan gejala-gejala lain yang menyebabkan ketidakstabilan sistem autonomi badan, tanggapan umum bahawa antipsikotik generasi kedua adalah lebih selamat serta ketiadaan ujian diagnostik piawai untuk mengesahkan NMS. Adalah diharapkan dengan menggunakan pendekatan yang sistematik serta kriteria yang dicadangkan sebagai panduan, doktor yang merawat mampu untuk mengesan penyakit ini pada peringkat yang lebih awal.

Kata kunci: *Agen antipsikotik; olanzapine; sindrom neuroleptik malignan*

ABSTRACT

Neuroleptic malignant syndrome (NMS) is rare and fatal. Unwanted complications can be prevented by early recognition and discontinuation of the offending medications, followed by aggressive treatment. We highlighted a case of a young gentleman with underlying schizophrenia, presented with altered mental state and hyperthermia after introduction of olanzapine. He developed NMS complicated by severe rhabdomyolysis and acute kidney injury. Although the patient had several findings suggestive of NMS, the diagnosis was not made promptly resulting in a delay in treatment. This may be due to the rarity of NMS, its resemblance to other causes of autonomic instability,

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the general knowledge that atypical antipsychotics are safer and unavailability of a gold standard diagnostic test for NMS. Using a systematic approach and existing criteria as a guide, treating doctors could be able to detect this disease early on.
Keywords: Antipsychotic agents; neuroleptic malignant syndrome; olanzapine

INTRODUCTION

Neuroleptic malignant syndrome (NMS) may be an uncommon encounter, but potentially life-threatening when it is not promptly recognised. Often missed due to overlapping symptoms with conditions causing autonomic instability, its mortality rate is estimated between 10 to 20% and could be higher when treatment is delayed (Shalev et al. 1989). While there are numerous reports on NMS related to first- and second-generation of antipsychotics, specific report on the near-miss cases is less frequently explored (Gurrera et al. 2017; Labuda & Cullen 2006; Zolezzi & Al-Hathloul 2002). We presented a near-miss case that highlighted the influence of anchoring bias on the recognition of NMS. This report details how to identify both classic and atypical NMS symptoms, offering management tips, especially helpful for emergency doctors.

CASE REPORT

A 35-year-old man with underlying schizophrenia who was previously on risperidone and aripiprazole, was admitted to a mental institute for aggressive behaviour. There was no reported complications from his previous antipsychotics. During this presentation, he was treated for relapsed schizophrenia and his medications were withhold while treatment with olanzapine 10 mg was initiated. After four days of treatment (D4), he began to experience bilateral hand tremors, rigidity and tachycardia. Intramuscular procyclidine and oral benzhexol were then prescribed. On the following day (D5), he developed high grade fever, and altered sensorium. In view of his progression and limited facilities in the mental institute, he was referred to the Emergency Department (ED).

At the ED, he appeared restless and confused. Blood pressure was 122/36 mmHg, pulse 130 beats/minute, temperature 40.2°Celsius, respiratory rate 40 breaths/minute, oxygen saturation of 98% and capillary sugar was 7.5 mmol/L. Examination of cardiovascular, respiratory and gastrointestinal systems were unremarkable. On central nervous system examination, the power of his bilateral upper and lower limbs was 4/5, hypertonic, reflexes were 1+, no clonus and Babinski were equivocal. The pupils were normal size. There was gross dark red colour urine in his urine bag.

He was treated for acute meningoencephalitis with intravenous ceftriaxone. The basic laboratory analyses revealed high white cell count of 19.1 $x10^9$/L, elevated of blood urea 23.9 mmol/L and creatinine 766.9 µmol/L. Other electrolytes were normal. Arterial blood gas showed metabolic acidosis with pH 7.37 and serum HCO_3 15.6 mmol/L, pCO_2 21mmHg, BE -16.9 mmol/L. The alkaline phosphatase was 2657 IU/L and alanine aminotransferase was 293 IU/L. The urine dipstick test showed pH 5, erythrocyte 5+, protein 3+, ketone 1+ and others were negative. Computed tomography (CT) brain showed changes suggestive of chronic infarct with no parenchymal lesion or intracranial bleed.

The initial diagnosis was later revised to acute rhabdomyolysis secondary to NMS, after being seen by the emergency physician. Serum creatine kinase was sent and markedly elevated with 256020 IU/L. He received intravenous fluid boluses, followed by a 24-hour high-volume fluid maintenance regimen that included urine and serum alkalinisation. Routine tepid sponging was performed and olanzapine was discontinued. For stiffness and agitation, intravenous midazolam was initiated and later changed to oral lorazepam 1 mg three times daily, which was gradually tapered as his agitation improved. Treatment with oral bromocriptine 2.5 mg three times daily was also administered for 5 days. He was admitted to the intensive care unit, and due to declining renal function and refractory hyperkalemia, hemodialysis was performed. Within a few days, his NMS symptoms successfully reversed. His agitation resolved, muscle rigidity and hyperthermia improved, and his creatine kinase (CK) levels showed a downward trend within the first week. He received several hemodialysis sessions due to acute kidney injury. After six weeks of hospitalisation, he was discharged with normal renal function and no longer required hemodialysis. He remained stable on oral lorazepam at discharge, and no antipsychotic medication was reintroduced.

DISCUSSION

NMS occurs more frequently with first-generation antipsychotics (FGA), with an incidence ranging from 0.02% to 3.23% (Ananth et al. 2004). In contrast, the incidence with second-generation antipsychotics (SGA) is lower (0.01% to 0.02%) though cases continue to be reported, with generally milder clinical presentations (Nakamura et al. 2012). It occurs more frequently in males, who are approximately 50% more likely to develop it, and generally affects young adults between the ages of 20 and 25, although it can appear at any age (Gurrera 2017). NMS may have a genetic component, as certain dopamine receptor gene variants are associated with its increased susceptibility (Mihara et al. 2003). A more recent study also found that individuals with intellectual disabilities prescribed antipsychotic medications were three times more likely to develop NMS (incidence rate ratio 3.03, 95% CI 1.26-7.30, p=0.013) (Sheehan et al. 2017). Mortality is typically caused by complications such as cardiorespiratory failure, renal failure or disseminated intravascular coagulopathy.

The pathogenesis of NMS remains poorly understood, with theories often revolve around dopamine receptor blockade in different brain regions. Blockade in the hypothalamus can induce hyperthermia and dysautonomia, while disruption of nigrostriatal dopamine pathways may manifest as Parkinson-like symptoms, including rigidity and tremors (Henderson & Wooten 1981; Tanii et al. 1996).

The diagnosis of NMS can easily be missed. This is because NMS exhibits symptoms overlapping to other conditions causing autonomic instability, including thyroid storm, pheochromocytoma, sympathomimetic toxicity, malignant catatonia, CNS infection and heatstroke. Other potential contributor to the diagnostic error is anchoring bias, a cognitive tendency notably prevalent in clinical practice, particularly within emergency medicine (Dargahi et al. 2022; Saposnik et al. 2016). In this case, the preliminary information provided by the first referring doctor did not emphasise the possibility of NMS, despite reports of hand tremors and rigidity. Instead, the history of fever and altered mental state became the focal points, leading to an impression of possible meningoencephalitis. This caused the initial attending ED doctor to lean towards the same diagnosis. When cognitive bias is

present, a doctor may overlook obtaining a comprehensive history, including past medical and medication details, resulting in a narrowed focus on more common diagnosis.

Before being admitted to the mental health facility, our patient had been taking risperidone and aripiprazole without showing any signs of NMS. However, after being admitted for a relapse of schizophrenia and started with olanzapine, he developed symptoms of NMS. This raises the likelihood of olanzapine-induced NMS, although his symptoms appeared much sooner than the usual 23-day onset period (Tse et al. 2015). Various reports have identified factors that may increase a patient's susceptibility to developing NMS, such as rapid dose escalation, cumulative dosage, parenteral administration, comorbidities, dehydration, prior agitation, brain injury, poorly controlled extrapyramidal symptoms, a family history of catatonia and previous episodes of NMS (Langan et al. 2012; Tse et al. 2015; Tural & Onder 2010). It is also essential to differentiate between NMS and serotonin syndrome (SS), as olanzapine also has serotonergic effect. While both NMS and SS share overlapping symptoms, SS typically has a more abrupt onset and is associated with hyperreflexia, clonus, and mydriasis, none of which were observed in this patient (Gurrera 2017).

There is no 'gold standard' diagnostic test for NMS. The Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) is commonly used to establish diagnostic criteria (Table 1) (American Psychiatric Association 2013). A multinational consensus group determined priority scores from DSM-5 criteria (Gurrera et al. 2011), with a study proposing a score of 74 as the threshold for diagnosing NMS (Gurrera et al. 2017), and our patient's score was 83. The use of scoring systems like this can help doctors identify NMS earlier. However, NMS can still manifest atypically. Symptoms may deviate from the typical tetrad of fever, rigidity, altered mental status and autonomic dysfunction. Variations like gradual onset, lack of elevated temperature, or subtle mental alterations can be misleading (Picard et al. 2008). Blood tests are not specific for diagnosing NMS, but

TABLE 1: DSM-5 criteria for diagnosis of NMS

Criteria for diagnosis of NMS	Priority scoring (Gurrera et al. 2011)
Exposure to dopamine antagonist, or dopamine agonist withdrawal, within past 72 hours	20
Hyperthermia	18
Rigidity	17
Mental status alteration	13
Creatine kinase elevation	10
Sympathetic nervous system lability, defined as at least 2 of the following: Blood pressure elevation or fluctuation Diaphoresis Urinary incontinence	10
Hypermetabolism, defined as heart rate increase and respiratory rate increase	5
Negative work-up for infectious, toxic, metabolic, and neurological causes	7
	Total: 100

measuring CK levels can be useful in detecting complications such as rhabdomyolysis, which is associated with NMS. Although elevated CK levels may indicate muscle damage, they are not definitive for diagnosing NMS, particularly in patients who develop fever while on psychotropic medications (O'Dwyer & Sheppard 1993).

Treatment for NMS is individualised based on severity. Stopping the triggering agent is crucial, with supportive care addressing complications like dehydration and rhabdomyolysis, including fluid resuscitation and alkalinisation. Bromocriptine restores dopaminergic tone, while benzodiazepines like lorazepam address rigidity and agitation. Dantrolene, though potentially hepatotoxic, can alleviate hyperthermia and rigidity. Retrospective analyses suggest bromocriptine and dantrolene may hasten recovery and decrease mortality (Rosenberg & Green 1989). Electroconvulsive therapy (ECT) can be considered for severe cases of NMS, though its effectiveness lacks strong evidence. ECT is believed to work by increasing dopamine levels in the brain, adjusting neurotransmitter pathways to address catatonia, and resetting autonomic dysfunction to reduce hyperthermia and muscle rigidity (Morcos et al. 2019; Trollor & Sachdev et al. 1999).

CONCLUSION

In conclusion, this case emphasises the need for careful attention when treating psychiatric patients on antipsychotics, particularly with autonomic instability, where the DSM-5 criteria can assist in identifying NMS. Treating doctors should remain vigilant for atypical presentations, which may not follow the classic signs. To avoid cognitive errors like anchoring bias, especially in fast-paced emergency settings, it is crucial to resist forming conclusions solely based on common presentations or initial symptoms that have a wide range of potential causes. A thorough review of the patient's psychiatric and medication history, along with considering alternative diagnoses, can significantly improve diagnostic accuracy and lead to better outcomes.

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