Neuroleptic Malignant Syndrome: The Value of Diagnostic Criteria

To the Editor: Neuroleptic malignant syndrome (NMS) is a rare but potentially serious reaction to antipsychotic medications. The incidence of NMS is around 0.9%,[1] with an estimated mortality of 5.6%–12%.[2,3] Early recognition is key and a low index of suspicion is required as the presentation shares symptoms with other disorders,[1,4,5] which is further compounded by a lack of definitive diagnostic criteria.

Case report. Mr A, an African man in his mid-20s, was admitted to an inpatient mental health unit in January 2017 with first-episode psychosis and was compulsorily detained under Section 2 of the UK Mental Health Act 1983. He appeared thought disordered, with derailment, tangentiality, thought blocking, and poverty of speech. He had no previous psychiatric history and no medical comorbidities. There was no family history of mental illness and no history of illicit drug use. Routine blood test results were unremarkable, and a urine drug screen was negative for all substances.

After admission to the ward, he began hitting his head against windows and was started on lorazepam 1 mg oral and haloperidol 5 mg oral on an as-required basis up to a maximum dosage of 20 mg/d. On day 3, following his third dose of haloperidol 5 mg, he began to show a marked improvement, being able to speak fluently and provide a good history of events. The haloperidol prescription remained on an as-required basis while monitoring for side effects in line with national guidance for management of first-episode psychosis,[6] and the patient received a maximum of 10 mg of haloperidol within a 24-hour period.

On day 4 of his admission, he began to experience upper limb stiffness following a fifth dose of haloperidol and became drowsy and disoriented. His physical examination showed an aural temperature of 37.7°C (99.9°F), tachycardia, and hypertension (Table 1). Haloperidol was discontinued immediately. After 1 hour, his symptoms appeared to improve and his vital signs were normalizing. However, 2 hours later, a clinical examination revealed marked upper and lower limb rigidity, and laboratory studies demonstrated a high creatine kinase (CK) level of 2,694 U/L (laboratory reference range, 30–175 U/L).

He was transferred to the medical ward for supportive management of NMS. He received fluids and lorazepam intravenously, and following improvement, he returned to the psychiatric ward 4 days later. He continued to improve, and aripiprazole was initiated 14 days after resolution of NMS to treat his psychotic symptoms. Aripiprazole was introduced from a low dose of 5 mg and slowly increased over 4 weeks to 15 mg at discharge. He experienced no recurrence of NMS and remains in remission under the care of the early intervention team in the community.

Multiple criteria for NMS have been reported,[7–13] each with differing critical values required to confirm the diagnosis. Gurrera et al[14] developed international consensus on criteria and critical values required to diagnose NMS. While this is a welcome attempt to achieve uniformity in diagnosis, difficulties remain in identifying how many criteria are required for a confident diagnosis.

In the case presented here, the patient met all criteria for NMS defined by Gurerra et al[14] except temperature over 38°C (100.4°F).

Table 1. Vital Signs Over the Course of Admission

		Day 4		
Characteristic	Day 1	1 PM	2 PM	4 PM
Temperature, °C (°F)	36.9 (98.4)	37.7 (99.9)	37.3 (99.1)	37.5 (99.5)
Respiratory rate	17	21	20	18
Oxygen saturation (%)	100	97	98	100
Heart rate	66	122	88	93
Blood pressure (mm Hg)	126/76	163/100	129/84	125/79

He would not have reached the threshold for diagnosis using several other criteria,[9,10,12] while those requiring temperature over 37.5°C (99.5°F) would have supported a diagnosis of NMS.[7,8,11] This case highlights the need for clinicians to be vigilant even when the full criteria are not met, as patients may not present with hyperthermia until later in the development of NMS[1,15] and cases of atypical NMS have been reported without hyperthermia.[16]

It has been suggested that due to inaccuracy of temperature measurements, it is difficult to tell if NMS truly is a "hyperthermic syndrome" and what level of hyperthermia is necessary to reach diagnostic threshold.[17] In this scenario, NMS was identified only 4 days after starting antipsychotics, possibly before the development of true hyperthermia, and therefore failed to reach full diagnostic criteria.

Additionally, guidelines on antipsychotic rechallenge following NMS are lacking, in part because most antipsychotics, including atypicals, have been associated with NMS.[18] While the choice of antipsychotic does not appear to affect the success of a rechallenge following NMS,[19] there are reports[20] that aripiprazole can be used with success in recurrent NMS, possibly due to partial agonism at D_2 receptors, and this case demonstrates a further instance of its successful use.

Clinicians need to remain vigilant and pragmatic regarding the multiple diagnostic criteria for NMS. In a condition with a high mortality rate predominantly affecting young people, prompt treatment in suspected NMS should be prioritized. In the case described, treatment with aripiprazole achieved remission of psychotic symptoms without a recurrence of NMS.

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