Multiple episodes of NMS: overlap with malignant catatonia

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There is ongoing debate in the literature as to whether neuroleptic malignant syndrome (NMS) and malignant catatonia are distinct clinical entities or illnesses on the same spectrum. Here, Drs Hardy and Evans present a case which puts forward arguments for both sides of the debate and raises questions regarding further management of psychosis in patients who develop multiple episodes of NMS.

The subject of this case report is a gentleman in his 40s with an established diagnosis of paranoid schizophrenia. Over a period of several months he was diagnosed with NMS on three occasions and later had two further discrete episodes that were in keeping with malignant catatonia. The first presentation was suggestive of NMS. The patient had been taking flupentixol decanoate 400mg depot injection every two weeks for the past eight months and was also taking risperidone 4mg daily and sertraline, which he had been on for about two months. He was found immobile on the floor of his home one week after his depot had been administered. He had been incontinent of urine and had not eaten or taken his oral medication for the preceding two days.

Clinical finding	NMS episodes	Catatonic episodes
Serum CK	Markedly raised	Mildly raised
Antipsychotic medication	Symptoms arose in presence of depot or oral antipsychotic	Symptoms arose in absence of antipsychotic
Extrapyramidal symptoms	Muscle rigidity, tremor	Mild muscle rigidity and tremor
Autonomic symptoms	Tachycardia, diaphoresis	Tachycardia, diaphoresis
Change in mental state	Delirium	No delirium
Pyrexia	Present	Present
Catatonic symptoms	No catatonic symptoms	Immobility, posturing, psychomotor retardation, poverty of speech

Table 1. Summary of clinical findings

On examination the patient was delirious with mild cogwheel rigidity and a low grade pyrexia. He was admitted to a medical ward, where a diagnosis of urinary sepsis was made and he was treated with intravenous antibiotics and fluids. Both NMS and serotonin syndrome were considered due to an elevated creatinine kinase (CK) of 20 972 U/L, for this reason the antidepressant and risperidone were discontinued. In spite of this, the medical team were confident that the raised CK was as a result of urinary sepsis and prolonged immobility, rather than NMS. He was administered depot antipsychotic medication within two weeks of this presentation. Six days later, he developed symptoms of delirium, diaphoresis, tremor and muscle rigidity. His CK was raised at 1559 U/L (having normalised between episodes). He was diagnosed with NMS, which was treated with intravenous fluids and his depot was discontinued. He was commenced on oral quetiapine about 10 days later, after the CK level had returned to the normal range.

Two weeks after initiating quetiapine he presented again with diaphoresis, mild pyrexia, tremor, muscle rigidity and tachycardia. He was described as perplexed but not delirious. His CK was measured at 8000 U/L, having remained in the normal range one week after initiation. He was treated on a medical ward for NMS with intravenous fluids and all neuroleptics were discontinued.

Within seven days, whilst completely medication free, he presented with periods of

immobility, posturing, psychomotor retardation, poverty of speech and drooling of saliva. His blood pressure, pulse and temperature were in normal range. He had very mild rigidity in his upper limbs and a mild tremor. He was treated for catatonia with lorazepam and appeared to have recovered fully within 24 hours. His CK was not measured on this occasion but was within the normal range the day before he developed catatonic symptoms.

There was a further catatonic episode three days later with similar symptoms with the addition of tachycardia and diaphoresis. He was on no antipsychotics at this time. His CK was elevated at 738 U/L. He was treated again with lorazepam for catatonic symptoms and made a full recovery within 24 hours. NMDA receptor autoantibodies were negative.

He has remained mentally stable without the use of antipsychotics and there have been no further catatonic episodes. The clinical findings of the case have been summarised in Table 1.

Discussion

This case demonstrates the initial development of NMS on high dose antipsychotic medication, a known risk factor.[1] The second episode of NMS is likely to have developed due to an insufficient washout period before recommencing an antipsychotic as the first episode was not recognised as NMS at the time. The recommended washout period for recommencing neuroleptics post-NMS has been suggested as at least two weeks,[2] but this may need to be extended for depot medication, which by its nature is longer acting.

Use of injectable antipsychotic medication is a known risk factor for NMS,[1,3] therefore the depot was discontinued following the second episode and a second generation antipsychotic was chosen to replace it due to lower risk of mortality from NMS.[4]

One condition, or two?

Due to the differing symptomatology of the NMS episode and the malignant catatonia episode, this case could demonstrate that the two conditions are separate entities. It could also be considered that due to multiple episodes of both syndromes appearing in this case that there may be a similar underlying pathology and the two conditions could be considered to be on a spectrum. The evidence supporting both possibilities are presented in Table 2.

Investigations

Elevated CK levels may have limited usefulness in terms of distinguishing between these two conditions. A rise in CK has been widely reported in NMS and also occurs in catatonic patients.[15]

Although NMDA receptor autoantibodies tested negative in the above case, there have been cases of patients with both catatonia and NMS testing positive,[16] which has important implications for management. Rickards et al. recommended screening for NMDA receptor

	Evidence favouring NMS and malignant catatonia being separate diagnostic entities	Evidence against NMS and malignant catatonia being separate diagnostic entities
Symptomatology	• Muscular rigidity is a consistent feature of NMS whereas literature from the pre-neuroleptic era suggested that muscular rigidity in malignant catatonia appeared as a later sign[5] • Different mode of onset of the two conditions: malignant catatonia often beginning with psychotic excitement leading to fever, exhaustion and death, whereas NMS often begins with severe extrapyramidal symptoms[6]	• Similar signs, symptoms and response to treatment,[8,9] individuals have been found to meet the diagnostic criteria for both conditions simultaneously[10] • Several reported cases of catatonia immediately preceding NMS,[11,12,13] which may suggest a common neurological basis for both conditions and that catatonia may sensitise individuals to the development of NMS[12] or may be a risk factor for the development of NMS[14]
Proposed mechanism of action	• Symptoms of NMS have been hypothesised to arise from D2 blockade in the striatum and abnormal cortical-subcortical modulation. This is in contrast to catatonic symptoms arising from right posterior parietal and lateral orbitofrontal dysfunction[7]	• Catatonia is a result of massive dopamine blockade due to excessive hyperstimulation in psychotic illness, whilst NMS is caused by a similar blockade but triggered by neuroleptics[12]

Table 2. Comparing evidence for and against NMS and malignant catatonia being different diagnostic entities

autoantibodies where 'red flag' symptoms, including catatonia and suspected NMS, are present in a psychotic patient.[17]

Management

This case raises the question of how to safely treat psychosis in the context of multiple episodes of NMS. The rate of recurrence of NMS has been reported as 30–50%.[18]

However, it has also been reported that as many as 87% may be successfully rechallenged with an antipsychotic following an episode of NMS.[2] A longer washout period has been found to increase the likelihood of success of rechallenge.[2,18] In one study of patients with a history of NMS, six out of nine patients were successfully treated with clozapine without any further complications.[19]

Clozapine induced NMS

It is important to consider that NMS induced by clozapine may present with fewer clinical features,[20] in particular, less rigidity and other extrapyramidal symptoms. Therefore clozapine-induced NMS may be particularly difficult to detect given that tachycardia, blood pressure disturbance and pyrexia are common during clozapine initiation due to the effects of clozapine itself or medical complications.[4]

Conclusion

This case demonstrates differing symptomatology of episodes of NMS and malignant catatonia, suggesting the two could be separate conditions. However, it does appear that one condition may increase susceptibility to developing the other.

The literature suggests that patients with catatonia appear to be at a higher risk of developing NMS and this case raises the question as to whether the reverse also holds true. This has implications for use of antipsychotics in catatonic patients and raises the question of whether there is a need for a 'symptom-free period' similar to the antipsychotic washout period for NMS before commencing an antipsychotic.

In similar complex cases NMDA receptor autoantibodies should be measured to rule out an underlying organic pathology.

There is currently little evidence to guide management of psychosis in a patient who has had multiple episodes of NMS, it seems that clozapine may be the most appropriate choice.

Due to the potential difficulties in detecting NMS in clozapine patients, we would suggest cautious dose titration with regular measurement of CK during the initiation period.

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Declaration of interests

No conflicts of interest were declared.

References

1. Keck PE, Pope HG, Cohen BM, *et al*. Risk factors for neuroleptic malignant syndrome. A case-control study. *Arch Gen Psychiatry* 1989;46(10):914–8.
2. Rosebush PI, Stewart TD, Gelenberg AJ. Twenty neuroleptic rechallenges after neuroleptic malignant syndrome in 15 patients. *J Clin Psychiatry* 1989;50:295–8.
3. Viejo LF, Morales V, Punal P, *et al*. Risk factors in neuroleptic malignant syndrome. A case-control study. *Acta Psychiatr Scand* 2003;107(1):45–9.
4. Trollor JN, Chen X, Chitty K, *et al*. Comparison of neuroleptic malignant syndrome induced by first and second generation antipsychotics. *Br J Psychiatry* 2012;201:52–6.
5. Mann SC, Caroff SN, Bleier HR, *et al*. Lethal catatonia. *Am J Psychiatry* 1986;143(11):1374–81.
6. Castillo E, Rubin RT, Holsboer-Trachsler E. Clinical differentiation between lethal catatonia and neuroleptic malignant syndrome. *Am J Psychiatry* 1989;146:324–8.
7. Northoff G. Catatonia and neuroleptic malignant syndrome: psychopathology and pathophysiology. *J Neural Transm* 2002;109:1453–67.
8. Fink M. Neuroleptic malignant syndrome and catatonia: One entity or two? *Biol Psychiatry* 1996;39:1–4.
9. Fink M, Taylor MA. The many varieties of catatonia. *Eur Arch Psychiatry Clin Neurosci* 2001;251:8–13.
10. Koch M, Chandragiri S, Rizvi S, *et al*. Catatonic signs in neuroleptic malignant syndrome. *Compr Psychiatry* 2000;41(1):73–5.
11. White DA. Catatonia and the neuroleptic malignant syndrome – a single entity? *Br J Psychiatry* 1992;161:558–60.
12. Osman AA, Khurasani MH. Lethal catatonia and neuroleptic malignant syndrome. A dopamine receptor shut-down hypothesis. *Br J Psychiatry* 1994;165: 548–50.
13. White DAC, Robins AH. Catatonia: Harbinger of the neuroleptic malignant syndrome. *Br J Psychiatry* 1991;158:419–21.
14. Berardi D, Amore M, Keck PE Jr, *et al*. Clinical and pharmacologic risk factors for neuroleptic malignant syndrome: a case-control study. *Biol Psychiatry* 1998;44(8):748–54.
15. Northoff G, Wenke J, Pflug B. Increase of serum creatine phosphokinase in catatonia: an investigation in 32 acute catatonic patients. *Psychol Med* 1996; 26:547–53.
16. Kiani R, Lawden M, Eames P, *et al*. Anti-NMDA-receptor encephalitis presenting with catatonia and neuroleptic malignant syndrome in patients with intellectual disability and autism. *BJPsych Bull* 2015;39: 32–5.
17. Rickards H, Jacob S, Lennox B, *et al*. Autoimmune encephalitis: a potentially treatable cause of mental disorder. *BJPsych Advances* 2014;20:92–100.
18. Wells AJ, Sommi RW, Crismon ML. Neuroleptic rechallenge after neuroleptic malignant syndrome: case report and literature review. *Drug Intell Clin Pharm* 1988;22:475–80.
19. Weller M, Kornhuber J. Clozapine rechallenge after an episode of 'neuroleptic malignant syndrome'. *Br J Psychiatry* 1992;161:855–6.
20. Karagianis JL, Phillips LC, Hogan KP, *et al*. Clozapine-associated neuroleptic malignant syndrome: two new cases and a review of the literature. *Ann Pharmacother* 1999;33(5):623–30.