



Neuroleptic malignant syndrome: A review of the clinical/diagnostic features and report of a case without fever

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ABSTRACT

Neuroleptic malignant syndrome (NMS) is an uncommon but potentially fatal idiosyncratic reaction characterized by the development of altered consciousness, hyperthermia, autonomic dysfunction, and muscular rigidity on exposure to antipsychotic (or some other psychotropic) medications. It is a medical emergency that requires early prompt identification and intervention. Fever is a predominant symptom in NMS. However, there have been reports that the classical high temperature usually associated with NMS may, on rare occasions, be absent.

Case presentation

This review and case report focus on the clinical/diagnostic features of NMS and a report of an unusual case without the classical high grade fever in a 27-year old male patient with schizophrenia who had been on high doses of multiple typical and atypical antipsychotic drugs.

Conclusion

This case report serves to remind clinicians of the essential features in the diagnosis of NMS and supports earlier reports that the classical high temperature usually associated with NMS may, on rare occasions, be absent and that would not exclude the diagnosis.

Keywords: Neuroleptic Malignant Syndrome, Clinical/Diagnostic Features, Fever

INTRODUCTION

Neuroleptic malignant syndrome (NMS), first identified in 1960 by Delay and colleagues during early trials of haloperidol,¹ is a rare but severe, life-threatening but almost certainly underdiagnosed² complication of neuroleptic therapy. It is an uncommon, acute, potentially fatal, idiosyncratic reaction to neuroleptic medications (primarily antipsychotics); the principal manifestations being due to disorders of thermoregulation and skeletal muscle metabolism mediated via central mechanisms.³

NMS has a relative high mortality outcome compared to common psychiatric conditions. Psychotropic medications such as the typical and atypical^{4,5} antipsychotics, certain dopamine receptor-blocking drugs used in the treatment of nausea and gastroparesis (e.g., promethazine, metoclopramide, prochlorperazine), and antidepressants like amoxapine have all been implicated in the aetiology of NMS.⁶ Another precipitant is the abrupt discontinuation of anti-Parkinsonian agents,⁷ and associations with the use of psychoactive substances such as cocaine⁴ and lysergic acid diethylamide² have been reported. Up to 0.02 – 3.2% of persons exposed

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to antipsychotics, especially the first generation antipsychotics, have been reported to develop NMS^{8,9} and mortality rates of as high as 10 – 30% have been reported among these victims.¹⁰⁻¹²

The disorder is characterized by severe hyperthermia, muscle rigidity, altered mental status and autonomic dysregulation, and laboratory findings such as elevated creatinine phosphokinase (CPK), leukocytosis, metabolic acidosis, and low serum iron or potassium levels.¹³ Although uncommon, NMS remains a critical consideration in the differential diagnosis of patients presenting with fever and mental status changes because it requires prompt recognition to prevent significant morbidity and death.¹⁴

Although neuroleptic malignant syndrome is easily recognized in its classic full-blown form, characterized by the presence of the triad of fever, muscle rigidity, and altered mental status, its presentation (and indeed onset, progression, and outcome) can be quite heterogeneous, as reflected in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) [DSM-IV] criteria (see Table 1).⁶ In the DSM-5, the description of neuroleptic malignant syndrome is expanded from that provided in DSM-IV-TR to highlight the emergent and potentially life-threatening nature of this condition.¹⁴ The clinical course typically begins with muscle rigidity followed by a fever within several hours of onset and mental status changes that can range from mild drowsiness, agitation, or confusion to a severe delirium or coma.¹⁵

CLINICAL FEATURES/DIAGNOSTIC CRITERIA

Prompt diagnosis and appropriate treatment will make the difference between the success and failure when treating a patient during the acute phase of neuroleptic malignant syndrome, NMS.¹⁶ If the index of suspicion is high, the risk associated with early intervention is minimal compared with the consequences of withholding treatment.

The diagnosis of NMS is often difficult because its manifestations can mimic that of other diseases. Various psychiatric/neurological classificatory systems have given guide on the clinical features that should be considered in making a diagnosis of NMS.

These include the 1994 APA DSM-IV (research criteria) code 333.92 (similar to the latest 2013 APA DSM-5, code 333.92); the 1992 WHO ICD-10, code G-21.0; and the 1993 Caroff-Mann criteria.

The diagnostic criteria established by Caroff and Mann (as adapted from Waldoff)¹⁶ include the following:

- 1) Hyperthemia (temperature, > 38°C);
- 2) Muscle rigidity;
- 3) Treatment with neuroleptics within 7 days of onset;
- 4) 5 of the following: change in mental status, diaphoresis or sialorrhoea, tachypnoea or hypoxia, tachycardia, hypertension or hypotension, incontinence, elevation of the creatine kinase level, myoglobinuria, leukocytosis, metabolic acidosis, tremor, and
- 5) Absence of drug-induced, systemic, or neuropsychiatric diseases.

The *Diagnostic and Statistical Manual of Mental Disorders* 4th Edition (DSM-IV) criteria for Neuroleptic Malignant Syndrome is represented thus in table 1 below.⁶

The ICD-10 describes it as a potentially fatal syndrome associated primarily with the use of neuroleptic agents which are in turn associated with dopaminergic receptor blockade in the basal ganglia and hypothalamus, together with sympathetic dysregulation and symptoms that include high fever, sweating, unstable blood pressure, confusion, and stiffness.¹⁷

Generalized rigidity, described as "lead pipe" in its most severe form and usually unresponsive to antiparkinsonian agents, is a cardinal feature of the disorder and may be associated with other neurological symptoms (e.g., tremor, sialorrhoea, akinesia, dystonia, trismus, myoclonus, dysarthria, dysphagia, rhabdomyolysis).¹⁷ Although several laboratory abnormalities are associated with NMS (such as elevated CPK, leukocytosis, metabolic acidosis, decreased serum iron concentrations, and elevations in serum muscle enzymes and catecholamines), no single abnormality is specific to the diagnosis.^{17,18}



Table 1 DSM-IV Diagnostic Criteria for NMS

A. Development of severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication.
B. Two (or more) of the following:
(1) Diaphoresis
(2) Dysphagia
(3) Tremor
(4) Incontinence
(5) Changes in level of consciousness ranging from confusion to coma
(6) Mutism
(7) Tachycardia
(8) Elevated or labile blood pressure
(9) Leukocytosis
(10) Laboratory evidence of muscle injury (eg, elevated CPK*)
C. The symptoms in criteria A and B are not due to another substance or a neurological or other general medical condition.
D. The symptoms in criteria A and B are not better accounted for by a mental disorder.

Abbreviation: *CPK = creatinine phosphokinase.

These criteria (Caroff-Mann, DSM-IV, and ICD-10) are highly related and in all, high fever or hyperthermia is a prominent feature. The latest (2013) edition of the APA manual – the DSM-5 - remarked that “hyperthermia (> 100.4°F or > 38°C on at least two occasions, measured orally), associated with profuse diaphoresis, is a distinguishing feature of neuroleptic malignant syndrome... Extreme elevations in temperature, reflecting a breakdown in central thermoregulation, are more likely to support the diagnosis of neuroleptic malignant syndrome.”¹⁷

Despite these established clinical manifestations of NMS, some researchers have reported NMS with the absence of at least one of the key or ‘typical’ features such as muscle rigidity,¹⁹ elevated CPK²⁰ or high fever.²¹⁻²⁴

CASE REPORT

We report a case seen and managed in our centre in March, 2016. Our patient, XY, was a young man, aged 27 years that had been battling with schizophrenia for 14 years. Until 4 months prior to presentation in our centre, he never received any orthodox treatment. Instead, he had sought care severally from herbal homes and prayer houses since the onset of his ailment in 2002. In the last prayer house he attended

before presenting to us, he was, besides being prayed for, placed on some drugs, mainly antipsychotics. It was gathered that an untrained personnel was administering drugs to patients in that prayer house. XY was placed on daily doses of oral chlorpromazine 900mg, risperidone 4mg, haloperidol 20mg, and benzhexol 5mg. He was retained in the prayer house for 60 days before the family opted to go home due to financial constraints. However, on leaving the prayer house, maintenance of his personal hygiene had improved and he was no longer aggressive but he was still talking to self and, in clear consciousness, hearing voices of unseen persons running commentary on his actions as well giving him commands from time to time. At home, XY continued to take these drugs but after five weeks of his return, the risperidone and benzhexol finished. He continued with chlorpromazine and haloperidol.

The onset of the problem that brought him to our centre was about two weeks after the risperidone and benzhexol got exhausted. He presented to us with a progressive stiffening of the body, inability to talk audibly, excessive sweating, and excessive drooling of saliva all of 10, 7, 5 and 3 days duration, respectively. Other features reported were occasional mutism, inability to swallow food freely, tremor both hands, and urinary incontinence.



As the body stiffness worsened to the extent of being unable to walk together with difficulty in swallowing food, his family took him to a Catholic hospital near his community from where he was referred to our centre.

There was no history of fever, headache, seizure, head trauma, or use of any psychoactive substance and other drugs. Also, XY had never reported any food allergies. However, he had had three episodes of generalized seizure, the first being 15 years ago and the last being three years prior to presentation to our hospital. There was no other significant past medical history.

XY was fairly kempt but ill-looking with a frightened gaze at the time of initial assessment. He was found to sweat a lot as well as urinate on self. He had generalized rigidity of the classical lead-pipe type and he was also moderately dehydrated. His speech was incomprehensible though he could respond to questions with signs. He had significant skin pallor more obvious in the palms and feet. He was not in any respiratory distress and was neither jaundiced nor cyanosed. He had no pedal oedema or peripheral lymphadenopathy.

His vital signs showed a pulse of 90 beats/min, a blood pressure of 120/75mmHg, oral temperature of 36.5°C, and a respiratory rate of 20 cycles/min. Findings on the respiratory, cardiovascular, gastrointestinal, and musculo-skeletal systems examinations were essentially normal. There were no signs of meningeal irritation.

Initial laboratory investigations showed serum creatinine phosphokinase of 100 IU/L (60 – 174 international units per litre of blood), total white blood cell count of 6,000/mm³ (5,000 – 10,000/mm³), neutrophil count of 8,500/mm³ (2,500 – 8,000/mm³), red blood cell (RBC) count 344 × 10⁴/mm³, a PCV of 33% (40 – 45%), and haemoglobin of 11.4g%. The liver function test, serum cholesterol, serum electrolyte/urea/creatinine, random blood sugar, blood culture, thyroid function test, serological testing for syphilis, and cerebrospinal fluid analysis showed no abnormality. Urine and blood toxicology tests did not support that patient had a recent

exposure to a psychoactive substance, an antidepressant, a non-steroidal anti-inflammatory drug, or an antiemetic like metoclopramide. Electroencephalographic and chest X-ray investigations were essentially normal and retroviral screening gave a negative result.

A diagnosis of neuroleptic malignant syndrome was made. XY was subsequently admitted into the hospital intensive care unit. All his earlier medications were discontinued. He was catheterized and his fluid input and output monitored. A skeletal muscle relaxant, dantrolene and a dopamine agonist, bromocriptine were administered in view of the severe muscle rigidity. Intravenous fluid (5% dextrose saline) was used to rehydrate patient. A nasogastric tube was passed for his oral medications and feeding. A nurse at each duty shift in the intensive care unit was specifically assigned to monitor and chart his vital signs.

The second day into his admission, the vital parameters remained normal but creatinine phosphokinase (CPK) levels increased from 100U/L to 2,700U/L. He remained mute within the first two days of admission. On the third day, he started making incomprehensible sounds but rigidity, sweating, skin pallor, and tremor continued to increase in severity and the CPK level increased further to 4,500U/L while the level of consciousness continued to fluctuate though temperature, pulse rate, and blood pressure remained normal. Urinary incontinence worsened on the third day. On the fourth day, he appeared better rehydrated. Fluid balance remained satisfactory all along. Urine analysis revealed myoglobinuria and a repeat serum electrolyte showed low potassium, 2.0mmol/L (3.5 – 5.0mmol/L). By the 10th day of his admission, rigidity appeared to have subsided a little, he started tolerating semi-liquid feeds orally, consciousness remained fairly stable, and he was able to sit down for some minutes without support. In the night of day 10, a complete blood count showed a leucocyte count of 12,000/mm³. Same night, his pulse rate was 140 beats/minute while the blood pressure fluctuated between 120/75mmHg and 160/90mmHg. An antibiotic was introduced into his drug regimen.



By the 11th day pulse and BP had normalized, his condition generally continued to improve gradually and the CPK level began to decrease, down to 400 U/L by the 13th day. He was transferred to the psychiatric ward on the 14th day. However, on the 18th day of admission, he reported resumed hearing of voices of unseen persons in clear consciousness giving him commands. The family objected to electroconvulsive therapy (ECT) and olanzapine, 2.5mg daily was gradually introduced from the 20th day. He was discharged home after two weeks of the olanzapine therapy (on the 34th day of admission) with the dose increased to 5mg nocte before discharge. At the time of discharge, he was generally stable though still had slight rigidity noticeable only in the upper limbs but he no longer had auditory hallucination. As at the time of compiling this report, he had been reviewed five times in our outpatient clinic and had remained progressively stable.

DISCUSSION

The normal adult male oral temperature is about 35.7–37.7 °C (96.3–99.9 °F). Hyperpyrexia (temperature above 38°C) is reported in virtually all cases of NMS.²³ The maximum temperature recorded in our patient was 37.2°C. Our patient was never pyretic all through the time he was on admission.

Elevated temperature of above 38°C is a major criterion for NMS in virtually all the classificatory systems. Taking the DSM-IV-TR or DSM-5TM for instance, our patient had a major feature of rigidity – the classical lead-pipe type. He also had seven of the ten features (with a minimum of two being required) in category B - diaphoresis, dysphagia, tremor, urinary incontinence, changes in level of consciousness, mutism, and elevated CPK as a laboratory evidence of muscle injury. Other autonomic dysfunctions noted include skin pallor and sialorrhoea.

Many medical conditions can mimic the presentation of NMS. One of these is central nervous system (CNS) infection.¹⁵ Since the patient did not show headaches, meningeal signs, or focal neurological signs, he is unlikely to have had a CNS infection. Lethal catatonia is associated with laboratory changes but with obvious hyperthermia. Parkinson's

disease is associated with rigidity but no elevated CPK. Diaphoresis may occur in endocrinopathies like thyrotoxicosis and phaeochromocytosis but CPK is usually normal and there is usually no lead-pipe rigidity. Rigidity is typical of severe extra-pyramidal symptoms but CPK usually remains normal. Systemic infection plus extrapyramidal symptoms may appear identical to NMS but CPK may not be elevated and culture usually shows evidence of infection. Serotonin syndrome also share some features with NMS, such as rigidity, tremor, sweating but hyperpyrexia may occur and there must be a history of exposure to an antidepressant of the selective serotonin reuptake inhibitor group.

Few researchers have reported cases of NMS without (or with delayed) fever. Anelopoulos et al reported a 31-year-old Caucasian male who developed NMS and whose temperature was 37.0°C throughout the episode.²⁵ Lev and Clark in 1994 reported a case of NMS without the characteristic initial onset of fever.²¹ The patient was on lithium and trilacon (perphenazine) before presentation to the emergency department with altered sensorium, rigidity, drooling, and tachycardia. The patient remained afebrile for 9 hours in the emergency department. In 2006, Rodriguez and Dowell reported a case of NMS without fever in a patient who had schizophrenia and was given aripiprazole, an atypical antipsychotic medication.²³ Four years later, Assareh and Habibi reported a case of a 41-year old man who developed afebrile NMS two weeks after receiving a dose of 12.5mg fluphenazine decanoate injection.²⁴ Peiris and colleagues had earlier reported three cases of patients who had all the features of NMS apart from fever and they responded well to bromocriptine.²²

It is evident that our patient had neuroleptic malignant syndrome. He did not have hyperpyrexia. Unfortunately he had numerous risk factors for NMS such as: high potency typical anti-psychotics (900mg of chlorpromazine plus 20mg of haloperidol daily), rapid dose reduction (stoppage of the 4mg daily risperidone when it finished), abrupt withdrawal of anti-cholinergics (benhexol which got exhausted alongside risperidone), psychosis (schizophrenia), dehydration, electrolyte disturbances (hypokalaemia



that was noted on the 4th day of admission), and past history of seizure.

It is not certain the factors that affected the course of NMS to be presented without fever in our case. Once NMS features are observed, especially in a patient exposed to high potency antipsychotics, notwithstanding the number of major or minor symptoms observed, all precipitating drugs should be discontinued and supportive symptomatic measures adopted. Where possible, patient should be managed in an intensive care unit for proper monitoring and reduction of human trafficking that can increase infectious process. Fluid intake and output should be monitored and rehydration should be initiated early enough. In cases where there is fever, common causes of fever such as malaria in endemic areas like ours should be considered and all measures that lower temperature like cooling blankets as well as pharmacotherapy should be adopted. In our case, we had no need for cooling blankets because the temperature remained normal all through the admission period. In severe dysphagia, expert feeding method has to be instituted. That, we did via the nasogastric tube and by our trained ICU nurses. It has been reported that following the discontinuation of the offending agent and appropriate supportive measures, most patients would usually recover over 5 to 14 days.^{9,18} Our patient made marked improvement at about the 14th day but had to stay longer on admission because we had to recommence him on an antipsychotic just as he was coming out of the fatal NMS experience. Many clinicians would allow up to two weeks elapse after recovery before reinstating an antipsychotic. We were challenged by the re-emergence of auditory hallucination (commanding type) that we had to initiate antipsychotic therapy before discharge, though low dose of a comparatively less potent single **atypical** antipsychotic.

CONCLUSION

This case report supports earlier observations that the classical high temperature usually associated with neuroleptic malignant syndrome may on rare occasions be absent. It is important for clinicians to note that NMS can occur without the usual temperature characteristic. A delay in instituting

appropriate management protocol simply because of the absence of fever might lead to a regrettable consequence.

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