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Neuroleptic Malignant Syndrome: A Review for Neurohospitalists

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Abstract

Neuroleptic malignant syndrome (NMS) is a life-threatening idiosyncratic reaction to antipsychotic drugs characterized by fever, altered mental status, muscle rigidity, and autonomic dysfunction. It has been associated with virtually all neuroleptics, including newer atypical antipsychotics, as well as a variety of other medications that affect central dopaminergic neurotransmission. 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. Treatment includes immediately stopping the offending agent and implementing supportive measures, as well as pharmacological interventions in more severe cases. Maintaining vigilant awareness of the clinical features of NMS to diagnose and treat the disorder early, however, remains the most important strategy by which physicians can keep mortality rates low and improve patient outcomes.

Keywords

neuroleptic malignant syndrome, movement disorders, neurohospitalist

Background

Neuroleptic malignant syndrome (NMS) is a severe disorder caused by an adverse reaction to medications with dopamine receptor-antagonist properties or the rapid withdrawal of dopaminergic medications. The first reported case of NMS appeared in 1956, shortly after the introduction of the antipsychotic drug chlorpromazine (thorazine).[1] Additional case reports quickly followed, and in a 1960 study French clinicians gave the syndrome its current name when they reported on the adverse effects of the newly introduced neuroleptic haloperidol and characterized a "syndrome malin des neuroleptiques."[2] Pooled data from 1966 to 1997 suggested the incidence of NMS ranges from 0.2% to 3.2% of psychiatric inpatients receiving neuroleptics[3]; however, as physicians have become increasingly aware of the syndrome and as newer neuroleptic agents have become available, the incidence has declined more recently to around 0.01% to 0.02%.[4] Although NMS occurs only rarely, it remains an unpredictable and potentially life-threatening neurologic condition that hospitalists must be able to recognize, as early identification and proper medical management are essential to ensure improved patient outcomes.

Clinical Presentation

The diagnosis of NMS is based on history and the presence of certain physical examination and laboratory findings.[5,6] Patients typically develop NMS within hours or days after exposure to a causative drug, with most exhibiting symptoms within 2 weeks and nearly all within 30 days.[7] Although NMS has classically been characterized by the presence of the triad of fever, muscle rigidity, and altered mental status, its presentation can be quite heterogeneous, as reflected in the current *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition [*DSM-IV*] criteria (see Table 1).[8] 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.

Signs of autonomic nervous system instability that frequently accompany NMS include labile blood pressure, tachypnea, tachycardia, sialorrhea, diaphoresis, flushing, skin pallor, and incontinence. Once symptoms appear, progression can be rapid and can reach peak intensity in as little as 3 days. Although muscle rigidity is the most frequently described motor sign, a large number of additional extrapyramidal motor

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Table 1. *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition [*DSM-IV*]) Research Criteria for Neuroleptic Malignant Syndrome[8]

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.

Table 2. Neuroleptic and Nonneuroleptic Medications Associated With Neuroleptic Malignant Syndrome

A. Neuroleptics	B. Nonneuroleptics with antidopaminergic activity
(1) Typical	(1) Metoclopromide
a. Haloperidol	(2) Tetrabenazine
b. Fluphenazine	(3) Reserpine
c. Chlorpromazine	(4) Droperidol
d. Prochlorperazine	(5) Promethazine
e. Trifluoperazine	(6) Amoxapine
f. Thioridazine	(7) Diatrizoate
g. Thiothixene	C. Dopaminergics (withdrawal)
h. Loxapine	(1) Levodopa
i. Perphenazine	(2) Dopamine agonists
j. Bromperidol	(3) Amantadine
k. Clopenthixol	(4) Tolcapone
l. Promazine	D. Others
(2) Atypical	(1) Lithium
a. Clozapine	(2) Phenelzine
b. Risperidone	(3) Dosulepin
c. Olanzapine	(4) Desipramine
d. Quetiapine	(5) Trimipramine
e. Ziprasidone	
f. Aripiprazole	

Abbreviation: NMS, neuroleptic malignant syndrome.

findings have been reported including tremor, chorea, akinesia, and dystonic movements including opisthotonos, trismus, blepharospasm, and oculogyric crisis.[3,9,10] Other symptoms that have been associated with NMS include dysphagia, dyspnea, abnormal reflexes, mutism, and seizures.[3,11-13]

Characteristic laboratory findings seen in NMS include elevated creatinine phosphokinase (CPK) due to rhabdomyolysis and leukocytosis, but these are neither specific for the syndrome nor present in all cases.[14] When rhabdomyolysis is present, it can be severe enough to cause renal failure, requiring hemodialysis.[13] Additional common laboratory abnormalities include a metabolic acidosis and iron deficiency.[15] The cerebrospinal fluid (CSF) and imaging studies are usually normal, but an electroencephalogram (EEG) may show nongeneralized slowing.[7]

Causative Agents

The primary trigger of NMS is dopamine receptor blockade and the standard causative agent is an antipsychotic. Potent typical neuroleptics such as haloperidol, fluphenazine, chlorpromazine, trifluoperazine, and prochlorperazine have been most frequently associated with NMS and thought to confer the greatest risk. Although atypical neuroleptics appear to have reduced the risk of developing NMS compared to typical neuroleptics,[10] a significant number of cases have been reported with most atypical neuroleptics including risperidone,[16] clozapine,[17] quetiapine,[18] olanzapine,[19] ariprazole,[20] and ziprasidone.[21] Neuroleptic malignant syndrome has also been associated with nonneuroleptic agents with antidopaminergic activity such as metoclopramide,[22] promethazine,[10] tetrabenzine,[23] droperidol,[24] diatrizoate,[25] and amoxapine.[26]

The abrupt cessation or reduction in dose of dopaminergic medications such as levodopa in Parkinson disease may also precipitate NMS.[27] The rapid switching from one type of dopamine receptor agonist to another in such patients has also been associated with NMS,[28] and there may be some risk of NMS associated with the abrupt withdrawal of Parkinson medications that are not known to have direct dopaminergic activity such as amantadine[29] and tolcapone.[30] Neuroleptic malignant syndrome has also been rarely associated with a number of other medications not known to have any central antidopaminergic activity such as lithium,[31] desipramine, trimipramine, dosulpin,[32] and phenelzine (Table 2).[33]

Differential Diagnosis

Many medical conditions can mimic the presentation of NMS, with some of the more common being heat stroke, central nervous system (CNS) infections, toxic encephalopathies, agitated delirium, status epilepticus, and more benign drug-induced extrapyramidal symptoms.[3,34] Heat stroke frequently presents with fever and altered level of consciousness, but it can be distinguished by a more abrupt onset and the more common presence of dry skin, hypotension, and limb flaccidity rather than extrapyramidal signs.[35] Importantly, neuroleptic medications can predispose patients to hyperthermia, making them prone to heat stroke, especially if contributing factors such as hot weather, dehydration, or excessive exercise or agitation are present.

Central nervous system infection must also be considered early in someone presenting with the clinical features of NMS to avoid any delay in the appropriate treatment. In

addition to fever and mental status changes, hallmarks of a CNS infection include a history of prodromal illness, headaches, meningeal signs, focal neurological signs, seizures, and frequently positive CSF and neuroimaging studies. If an infectious etiology is suspected, a lumbar puncture and blood, urine, and CSF cultures are mandatory, and an EEG may be required to rule out seizure activity.

Often complicating the diagnosis of NMS is the large number of drug-induced syndromes that can have motor and cognitive features that resemble the condition. The use of neuroleptic agents has been associated with a variety of adverse motor effects including parkinsonism, acute dystonia, acute akathisia, tremor, and tardive dyskinesia,[8] and several other classes of drugs at toxic levels may cause symptoms resembling NMS such as serotinergic agents, anticholinergics, monoamine oxidase inhibitors, tricyclics, lithium, meperidine, and fenfluramine.[36] Intoxication syndromes from drugs of abuse such as cocaine, amphetamine, methamphetamine, phencyclidine, and 3,4-Methylenedioxymethamphetamine (MDMA [aka Ecstasy]) can produce hyperthermia, mental status changes, and autonomic dysfunction and can easily be confused with NMS.[34] Abrupt withdrawal syndromes from alcohol and benzodiazepine can also be associated with altered mental status and muscle rigidity, and there is at least one report of a case of an NMS-like syndrome resulting from withdrawal of baclofen.[37]

Serotonin syndrome, which presents with altered mental status, autonomic changes, and motor features related to serotonin excess, shares a number of similarities with NMS.[38] Nevertheless, it can typically be distinguished by history, the absence of leukocytosis and elevated CPK, and the presence of gastrointestinal symptoms (eg, nausea, vomiting, and diarrhea) and motor features other than muscle rigidity such as tremor, ataxia, myoclonus, hyperreflexia.[39] Malignant hyperthermia, a severe drug-induced reaction linked to defective calcium-related proteins, may also present clinically like NMS. However, because it is triggered by potent inhaled anesthetic agents or depolarizing muscle relaxants, usually history alone is able to discern the two syndromes.[40]

Lethal catatonia is a life-threatening psychiatric disorder that can present with clinical features of fever, rigidity, akinesia, and altered mental status.[41] Although it can be difficult to distinguish it from NMS, the motor features in lethal catatonia are typically preceded by a few weeks of behavioral changes including ambivalence, apathy, withdrawal, automatisms, extreme negativism, and psychotic agitation.[42] As lethal catatonia typically requires neuroleptic treatment as opposed to being caused by such treatment, rapid clinical differentiation between these two disorders is extremely important (Table 3).

Pathophysiology

The underlying pathophysiologic mechanisms of NMS are complex and elements still debated among experts, but most agree that a marked and sudden reduction in central dopaminergic activity resulting from D2 dopamine receptor blockade within the nigrostriatal, hypothalamic, and mesolimbic/cortical pathways helps explain the clinical features of NMS including rigidity, hyperthermia, and altered mental status, respectively.[12,34] This theory is supported by the observation that the primary cause of NMS is the use of antipsychotic drugs that specifically block dopamine receptors, and in particular D2 receptors, and that the syndrome can also be induced by abrupt dopamine withdrawal. Additional support comes from a dopamine receptor imaging study of 1 patient with NMS demonstrating a complete lack of D2 receptor binding in the acute phase,[43] and another study showing low levels of the dopamine metabolite homovanillic acid in the CSF of patients with acute NMS.[44]

D2 dopamine receptor antagonism, however, does not explain all the presenting signs and symptoms of NMS, nor does it explain its occurrence with antipsychotic medications with lower D2 activity and medications without known antidopaminergic activity. This has led some to propose that sympathoadrenal hyperactivity, resulting from the removal of tonic inhibition within the sympathetic nervous system, may play a key role in the pathogenesis of NMS.[45] Abnormalities in the sympathetic system are supported by the frequent presence of autonomic symptoms in NMS as well as demonstrated changes in the urine and plasma catecholamine levels in patients with NMS. Some have hypothesized that NMS shares pathophysiological similarities with malignant hyperthermia and that a defect in calcium regulatory proteins within sympathetic neurons may be the key factor that brings about the onset of NMS.[46]

Another system that also appears to play a role in the signs and symptoms of NMS is the peripheral skeletal muscle system. Release of calcium has been shown to be increased from the sarcoplasmic reticulum of muscle cells with antipsychotic usage, possibly leading to increased muscle contractility and rigidity, breakdown of muscle, and hyperthermia.[12] To date, however, none of the theories put forth as the underlying cause of NMS have been able to explain why only a small fraction of patients exposed to neuroleptics develop the condition. Furthermore, it remains unknown why patients who develop NMS are usually able to continue being treated with similar medications and, at times, even the same offending agent.

Risk Factors

The main risk factors for developing NMS are the initiation or increase in dose of a neuroleptic medication and the potency and administration form of that drug.[47,48] The use of high-dosed, high-potency and long-acting or intramuscular depot forms of neuroleptics, as well as a rapid increase in dosage of neuroleptics, both increase the risk of developing NMS. The concurrent use of multiple neuroleptics, or concomitant taking of predisposing drugs such as lithium, also appear to

Table 3. Differential Diagnosis for Neuroleptic Malignant Syndrome

Differential Diagnosis	Distinguishing Features
Infectious	
(1) Meningitis or encephalitis	History of prodromal viral illness, headaches or meningeal signs
(2) Brain abscess	Presence of seizures or localizing neurological signs
(3) Sepsis	Brain imaging
(4) Rabies	CSF studies
Metabolic	
(1) Acute renal failure	Renal or thyroid function tests
(2) Rhabdomyolysis	Absence of neuroleptic treatment
(3) Thyrotoxicosis	Presence of severe hypertension
(4) Pheochromocytoma	Significantly elevated catecholamines and metanephrines
Environmental	
(1) Heat stroke	History of exertion or exposure to high temperatures
(2) Spider envenomations	Hot dry skin, skin lesion suggestive of spider bite
	Absence of rigidity
	Abrupt onset
Drug-induced	
(1) Malignant hyperthermia	History of inhalational anesthetics
(2) Neuroleptic-induced syndromes	Family history of malignant hyperthermia
a. Parkinsonism	Presence of hyperkinesias
b. Acute dystonia	Positive toxicology/drug-level screen
c. Acute akathisia	Low or normal CPK
d. Tardive dyskinesia	Presence of nausea, vomiting, diarrhea
e. Postural tremor	Presence of anticholinergic signs (dilated pupils, dry mouth, dry skin, urinary retention)
(3) Nonneuroleptic-induced syndromes	Presence of rash, urticaria, or eosinophilia
a. Serotonin syndrome	History of drug dependence, abuse, or overdosages
b. Anticholinergic delirium	
c. Monoamine oxidase inhibitor toxicity	
d. Lithium toxicity	
e. Salicylate poisoning	
f. Strychnine poisoning	
g. Drugs of abuse (cocaine, amphetamine, methamphetamine, MDMA, phencyclidine)	
Drug-withdrawal syndrome	History of drug dependence, abuse, or overdosages
(1) Alcohol	Absence of neuroleptic treatment
(2) Benziodiazepine	Toxicology screen
(3) Baclofen	
(4) Sedatives	
(5) Hypnotics	
Neurological or psychiatric disorder	Absence of fever or leukocytosis
(1) Parkinsonism	Presence of hyperkinesias, later emergence of rigidity
(2) Nonconvulsive status epilepticus	Prior history of catatonic states
(3) Lethal catatonia	Absence of neuroleptic treatment
	EEG
Autoimmune	Proximal weakness
(1) Polymyositis	Abnormal EMG or muscle biopsy
	Presence of cancer or interstitial lung disease

Abbreviations: CPK, creatinine phosphokinase; CSF, cerebrospinal fluid; EEG, electroencephalography; EMG, electromyography; MDMA, 3,4-Methylenedioxymethamphetamine.

confer an increased risk.[9,13] Although NMS can occur at anytime during neuroleptic treatment and no definite correlation between the duration of exposure to a neuroleptic and risk of developing the condition has been found, it is less likely to occur if a patient has been on a stable dose of their antipsychotics for a long period of time and there are no issues of noncompliance.[3,13]

A variety of other risk factors have emerged from epidemiological and case studies of NMS which include dehydration, physical exhaustion, exposure to heat, hyponatremia, iron deficiency, malnutrition, trauma, thyrotoxicosis, alcohol, psychoactive substances, and presence of a structural or functional brain disorder such as encephalitis, tumor, delirium, or dementia.[47-49] Males under 40 years are often thought to be at

greater risk of developing NMS as well, but it remains unclear whether this elevated risk is primarily due to the increased incidence of neuroleptic use in this population. Postpartum women may also be at slightly higher risk of developing NMS.[50] Reports of identical twins and a mother and 2 of her daughters all presenting with NMS suggest that a genetic risk factor for NMS may exist,[51] and some limited genetic investigations help support existence of genetic component to the condition,[46] possibly through a genetically associated reduction in the function of the D2 dopamine receptor.[52]

Treatment

Neuroleptic malignant syndrome in hospitalized patients is considered a neurologic emergency as a delay in treatment or withholding of therapeutic measures can potentially lead to serious morbidity or death. As such, some consider it prudent to treat for NMS even if there is doubt about the diagnosis.[53] Due to its rarity, however, systematic clinical trials in NMS are difficult to perform and so no evidence-based treatment approach exists. Nevertheless, effective general guidelines have been gleaned from case reports and analyses.[54]

Treatment of NMS is individualized and based on the clinical presentation, but the first step in essentially all cases consists of cessation of the suspected offending neuroleptic pharmacologic agent. If the syndrome has occurred in the setting of an abrupt withdrawal of a dopaminergic medication, then this medication is reinstituted as quickly as possible. The next key step in the management of NMS is the initiation of supportive medical therapy. Aggressive hydration is often required, especially if highly elevated CPK levels threaten to damage the kidneys, and treatment of hyperthermia with cooling blankets or ice packs to the axillae and groin may be needed. Metabolic abnormalities may need to be corrected, and bicarbonate loading should be considered in some cases as it may be beneficial in preventing renal failure.[55] Patients with NMS may be at increased risk of morbidity due to renal failure and disseminated intravascular coagulation (DIC) secondary to rhabdomyolysis,[34] deep venous thrombosis and pulmonary embolism resulting from dehydration and immobilization, aspiration pneumonia because of difficulty swallowing combined with an altered mental status, as well as other medical complications including cardiopulmonary failure, seizures, arrhythmias, myocardial infarction, and sepsis, and so many cases require intensive care monitoring and support.[3,13,56,57]

In more severe cases of NMS, empiric pharmacologic therapy is typically tried. The two most frequently used medications are bromocriptine mesylate, a dopamine agonist, and dantrolene sodium, a muscle relaxant that works by inhibiting calcium release from the sarcoplasmic reticulum. Anecdotal reports and meta-analyses suggest these agents may shorten the course of the syndrome and possibly reduce mortality when used alone or in combination.[58,59] Bromocriptine is given to reverse the hypodopaminergic state and is administered orally (or via nasogastric tube), starting with 2.5 mg 2 or 3 times daily and increasing doses by 2.5 mg every 24 hours until a response or until reaching a maximum dose of 45 mg/d.[13,34,58,59] Dantrolene can be administered intravenously starting with an initial bolus dose of 1 to 2.5 mg/kg followed by 1 mg/kg every 6 hours up to a maximum dose of 10 mg/kg/d.[13,34,58,59] Oral dantrolene is used in less severe cases or to taper down from the intravenous form after a few days with doses that range from 50 to 200 mg/d. Due to a risk of hepatoxicity, dantrolene is typically discontinued once symptoms begin to resolve. Bromocriptine, however, is generally maintained for at least 10 days for NMS related to oral neuroleptics and 2 to 3 weeks for depot neuroleptics.

Other dopaminergic agents besides bromocriptine have been used including amantadine hydrochloride,[60] levodopa,[61] and apomorphine.[62] Additional pharmacologic agents that may have some utility in treating NMS are benzodiazepines,[63] which can be helpful in controlling agitation but may also ameliorate symptoms and hasten recovery in milder cases, carbamezapine,[64] and clonidine.[65] In cases that do not respond to standard medical care, electroconvulsive therapy has been reported to improve some of the symptoms of NMS and may be effective.[66,67]

Recurrences of NMS do occur, especially when a patient is restarted on a neuroleptic with high potency or too quickly after their initial episode.[12,68,69] Most patients who require continued antipsychotic treatment, though, are able to have a neuroleptic safely reintroduced with proper precautions including very slow titration and careful monitoring after a waiting period of about 2 weeks for an oral neuroleptic and at least 6 weeks for a depot form.[14,70] Although NMS is considered an idiosyncratic reaction, it is generally felt to be prudent to use a different neuroleptic than the one that was originally associated with the development of the syndrome.[12,13,71]

Prognosis

Initial reports of mortality rates from NMS were over 30%, but increased physician awareness and introduction of newer neuroleptic medications over the last few decades have helped reduce them to closer to 10%.[71] When recognized early and treated aggressively, NMS is usually not fatal and a majority of patients will recover completely between 2 and 14 days.[3,7] But if diagnosis and treatment are delayed, resolution can require several weeks or longer, and surviving patients may have residual catatonia or parkinsonism, or significant morbidity secondary to renal or cardiopulmonary complications.[10,13,34] When death does occur, it is usually attributable to arrhythmias, DIC, or cardiovascular, respiratory, or renal failure. Thus, early recognition and initiation of therapeutic measures by physicians remain paramount to reducing the number of severe cases of NMS and limiting this significant source of morbidity and mortality among patients receiving antipsychotics.

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