Neuroleptic Malignant Syndrome: A Brief Review

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Neuroleptic malignant syndrome (NMS) is a rare, idiosyncratic disorder. As its name implies, NMS is a potentially lethal process related to the use of neuroleptic agents (eg, butyrophenones, phenothiazines, thioxanthenes) that produce dopaminergic blockade. NMS may occur in any patient taking a neuroleptic drug, regardless of the duration of use. The disorder is characterized by several cardinal features, including autonomic dysfunction, altered mental status, muscular rigidity, and hyperthermia.

Although relatively uncommon, NMS carries a significant mortality rate, which mandates early recognition and intervention; the disorder can present quite a clinical challenge in treating agitated patients who have both medical and psychiatric illnesses. NMS is of particular interest to emergency physicians because of its acute onset, its severity, and the fact that its mortality can be substantially reduced through prompt recognition and treatment. The disorder shares many clinical features with other hyperpyrexic disorders, including malignant hyperthermia, serotonin syndrome, lethal catatonia, environmental heat disorders, and infectious diseases.

This article will present an overview of NMS through discussion of the etiologic and pathophysiologic mechanisms that underlie the disorder. Special emphasis will be placed on the early recognition of NMS, including its atypical presentations, and the therapeutic measures available to the practicing clinician to avert some of the unfortunate complications of the disorder.

HISTORY AND EPIDEMIOLOGY

Neuroleptic medications were first introduced in 1954, and Delay and Deniker first described NMS in 1968.[1] The reported incidence of NMS ranges from 0.5% to 3% of patients taking neuroleptic drugs.[2] It occurs equally in men and women and has been reported in patients as young as 3 years and as old as 80 years. Most cases, however, occur in young and middle-aged adults, among whom the use of neuroleptic medications is greatest.[3] There is an asymmetric bimodal distribution of cases: the first and greater peak occurs in persons age 20 to 40 years and involves patients with schizophrenia taking neuroleptic agents as treatment of psychosis; the second and lesser peak occurs in patients older than 70 years who are on levodopa and/or neuroleptic drugs to control behavioral symptoms (especially agitation) of dementia or delirium.[4,5]

The mortality rate from NMS has been declining in recent years. Before 1984, the mortality rate was nearly 40%.[6] Since then, the mortality rate has decreased to 11.6%, which is still a quite significant number.[4] The decline in mortality rate has largely occurred because of earlier physician recognition and treatment of the disorder, in addition to newer and better critical care therapeutic modalities.

ETIOLOGY AND PATHOPHYSIOLOGY

NMS is believed to result from dopaminergic blockade or depletion in the central nervous system. Neuroleptic drugs block dopamine receptors in various areas of the central nervous system—including the hypothalamus, the corpus striatum, the basal ganglia, and spinal areas—with wide-ranging effects. Sudden and profound central dopaminergic blockade is the most favored hypothesis for the pathogenesis of NMS.[6] This hypothesis is supported by animal model studies.[4]

Theoretically, central dopaminergic blockade explains the clinical tetrad of symptoms seen in NMS. Muscle contraction and rigidity occur when dopamine effects are blocked in the corpus striatum. Subsequent muscle contraction generates a tremendous amount of heat energy peripherally and results in pyrexia. Pyrexia also occurs secondary to impaired heat dissipation when dopamine receptors are blocked in the thermoregulatory centers of the preoptic nuclei of the anterior hypothalamus. Mental status changes may be caused by dopamine receptor blockade in the nigrostriatal and mesocortical systems. Finally, dopamine receptor

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blockade at the level of the spinal cord may be responsible for the autonomic disturbances seen with NMS.[4,7]

Additional clinical support for the dopaminergic depletion theory of NMS is provided by the improvement of patients with NMS after treatment with dopaminergic agonists such as bromocriptine and amantadine. Furthermore, NMS resulting from temporary cessation of dopamine therapy in patients with Parkinson's disease may be readily reversed with a return to dopamine agonist therapy.[4,8]

NMS can develop with either initiation of neuroleptic therapy or a change in drug dosage. The risk for NMS can be increased by initiation of a neuroleptic therapy at high drug dosages, by rapid upward titration, by a change to higher potency neuroleptic agents, or by the use of long-acting depot preparations.[9] The onset of NMS is not related to the duration of neuroleptic exposure or to toxic overdoses. It can occur anywhere from a few hours to days after initiation of therapy or even several years after being on a stable dosage regimen.[7] Drug levels are often found to be therapeutic in most cases of NMS.[4,10] More than 25 pharmacologic agents have been implicated as triggers for NMS, most commonly butyrophenones, phenothiazines, and thioxanthenes. Haloperidol and fluphenazine have been the most commonly cited drugs, probably because of their widespread use and higher potency. Other agents—including tricyclic antidepressants, monoamine oxidase inhibitors, and lithium—have also been reported to cause NMS, perhaps through synergistic interactions or as yet undefined mechanisms.[4,10] **Table 1** lists drugs that have been cited as common triggers of NMS.

Some patients seem to have a predilection for NMS when treated with any dopamine antagonist. Others develop the disorder only when treated with specific dopamine antagonists. In some cases, reinstitution of neuroleptic therapy with the same drug following full recovery from NMS has been undertaken cautiously without further ill effects.[7,10,14,15] The likelihood that someone will develop NMS thus seems to be more dependent upon his or her physiologic state at the time of administration of the neuroleptic agent.[2,10,16,17]

Additional risk factors for NMS include high ambient temperatures and humidity, dehydration, concomitant illness, AIDS-related dementia, head trauma, a general debilitated state, and organic brain disease.[2,10,16,17] Clearly, given the idiosyncratic nature of the disorder, there are other factors that must play a role in NMS.

CLINICAL MANIFESTATIONS

NMS can present with a wide array of clinical manifestations, ranging from mild to severe. The diversity of its clinical features may not always be appreciated and may initially lead to diagnostic delay and confusion with other, more common diagnoses.[2,10,18] **Table 2** lists alternative diagnoses with which NMS is often confused. A history of psychiatric illness, particularly when accompanied by a history of phenothiazine or butyrophenone use, should always arouse suspicion of the disorder.

As previously suggested, the classic features of NMS include muscular rigidity, altered sensorium, autonomic instability, and hyperthermia (ie, temperature greater than 38°C [100.4°F]). The development of

Table 1. Drugs That Can Cause Neuroleptic Malignant Syndrome

Neuroleptic drugs
Butyrophenones
Phenothiazines
Thioxanthenes
Other dopamine antagonists
Hydroxyzine
Reglan
Reserpine
Nonneuroleptic drugs
Tricyclic antidepressants
Amitriptyline
Amoxapine
Desipramine
Maprotiline
Monoamine oxidase inhibitors
Phenelzine
Tranylcypromine
Benzodiazepines
Diazepam
Lorazepam
Anticonvulsants
Carbamazepine
Phenytoin
Dopaminergic medications temporarily withdrawn in patients with Parkinson's disease
Amantadine
Bromocriptine
Levodopa
Lithium

Data from Chan et al,[10] Heyland and Sauve,[11] Koehler and Mirandolle,[12] and Leverson.[13]

Table 2. Differential Diagnosis in Cases of Neuroleptic Malignant Syndrome

Endocrine system	
	Pheochromocytoma
	Thyrotoxicosis
Environmental insults	
	Heat stroke
Infections	
	Encephalitis
	Meningitis
	Rabies
	Sepsis
	Tetanus
Neuromuscular system	
	Malignant hyperthermia
	Severe dystonia
	Status epilepticus
Psychiatric conditions	
	Lethal catatonia
Toxic exposures	
	Amphetamines
	Anticholinergic agents
	Cocaine
	Excess serotonin (serotonin syndrome)
	Monoamine oxidase inhibitors
	Salicylates
	Strychnine
Miscellaneous causes	
	Alcohol or sedative withdrawal
	Autoimmune disorders
	Central nervous system infarction
	Central nervous system neoplasm

Data from Persing,[2] Chan et al,[10] Heyland and Sauve,[11] Levenson,[13] Brown et al,[19] LoCurto,[20] Chan et al,[21] Mills,[22] Demirkiran et al,[23] Ames and Wirshing,[24] and Johnson and Cunha.[25]

progressive muscular rigidity is an early major manifestation of impending NMS.[2] This symptom is often followed by the successive appearance of mental status changes, autonomic instability, and—almost invariably—hyperpyrexia. Taken together, these clinical features are nonspecific, and a suspicion of NMS may initially elude even the most astute clinician in favor of more common entities.[18]

Muscle rigidity in NMS is often described as “lead pipe” rigidity because of its strong resistance to passive movement. Other motor symptoms of muscle rigidity in NMS include akinesia, bradykinesia, cogwheeling, myoclonus, tremor, chorea, opisthotonos, dysarthrias, dysphagia, trismus, akathisias, and dystonias.[2,4,26] The muscular rigidity contributes to the underlying hyperthermia of the disorder and is usually associated with varying degrees of myonecrosis and rhabdomyolysis.[7,16,18,27,28]

Core temperature in patients with NMS generally ranges from 38.5°C (101.3°F) to 42°C (107.6°F).[16] Normothermic cases of NMS have been described, but they are extremely rare and are thought to represent milder forms of the disorder.[4,9,29] The severe hyperthermia occurring with NMS may also be encountered in several other clinically similar disorders (eg, drug fever, serotonin syndrome, sepsis, heat stroke)—all of which might initially confound a diagnosis of NMS.[7,25]

Mental status changes range from mild confusion and delirium to lethargy, stupor, and coma, although fluctuating levels of consciousness are most common.[2,4,26] In the classic case, a patient may appear alert but is actually dazed and mute, at times mimicking lethal catatonia.[9] Autonomic instability is manifested by tachycardia, labile blood pressure, tachypnea, profuse diaphoresis, cardiac dysrhythmias, sialorrhea, and incontinence.[2,4]

Unfortunately, there are no consistent diagnostic criteria for NMS, although some authors have proposed their own.[13,30] Instead, NMS is largely a clinical diagnosis and is made by exclusion in the appropriate setting. **Table 3** lists some of the commonly accepted clinical criteria used to support a diagnosis of NMS.

LABORATORY FINDINGS

Although no laboratory test is definitively diagnostic of NMS, a complete laboratory evaluation, along with meticulous history taking and physical examination, will aid the clinician in excluding other potentially life-threatening illnesses. Moreover, several laboratory studies are in fact supportive of the diagnosis and may even serve as early indices of potential complications of NMS.

The most useful clinical test is measurement of the creatine kinase (CK) level. The CK level will be increased in nearly all cases of NMS, sometimes dramatically, as a result of rhabdomyolysis from sustained muscle rigidity. The CK level is therefore a measure of the amount of myonecrosis that has occurred and is an indicator of potential acute renal failure secondary to myoglobinuria. Renal failure is one of the most common causes of death from NMS,[2] so excluding myoglobinuria in an essential step in dealing with the disorder.

Other less specific laboratory findings include a mild-to-moderate leukocytosis (leukocyte count, 15–30 × 10^3/mm^3) with a left shift and mild elevations in serum aminotransferase levels secondary to hyperpyrexia and fatty liver changes.[4,9,16] In addition, a metabolic (lactic) acidosis, hypoxemia, hypernatremia or hyponatremia, azotemia, myoglobinuria, and mild coagulopathies may also be present.[9,27] Interestingly, results of electrocardiography, electroencephalography, chest radiography, computed tomography of the head, and analysis of cerebrospinal fluid obtained on lumbar puncture show no abnormalities in uncomplicated cases of NMS.

COMPLICATIONS

Complications of NMS are numerous. The most universal complication is rhabdomyolysis resulting from sustained muscle rigidity and consequent muscle breakdown. Other common complications include renal failure, aspiration pneumonia, pulmonary embolism, pulmonary edema, adult respiratory distress syndrome, sepsis, disseminated intravascular coagulation, seizures, and myocardial infarction.[4] Death early in the course of NMS can occur from respiratory failure (secondary to chest wall rigidity and hypoventilation or to aspiration pneumonia) or from cardiac arrest. Later deaths are often the result of renal failure, refractory acidosis, or multiorgan failure.[2,3,6,16,27]

MANAGEMENT

As suggested earlier, proper treatment of patients with NMS demands the prompt recognition of the clinical disorder, including the exclusion of sepsis and other diagnostic possibilities, and the implementation of supportive care measures as well as specific pharmacologic interventions.[7] Specific management guidelines for NMS are outlined in **Table 4**.

Management of NMS always requires prompt discontinuation of the offending neuroleptic agent or reinstitution of dopaminergic therapy in patients with Parkinson's disease. Supportive care measures are the mainstay of treatment and include use of aggressive cooling, antipyretics, fluid and electrolyte repletion, and appropriate treatment of potential complications (eg, alkaline diuresis in cases of rhabdomyolysis).

Given the fact that profound dopaminergic blockade can be a primary causative factor of NMS, it seems logical to expect that restoration of central dopaminergic balance would facilitate recovery from fulminant NMS. Indeed, this theory serves as the foundation for some of the specific pharmacologic therapies for NMS.[2,4,6,7]

Table 3. Clinical Criteria for Diagnosing Neuroleptic Malignant Syndrome

Hyperthermia*

Oral temperature > 38°C (100.4°F) in the absence of another known cause

Extrapyramidal effects (2 or more)*

Choreiform movements
Cogwheel rigidity
Dyskinesia
Dysphagia
Festinating gait
Lead pipe muscle rigidity
Oculogyric crisis
Opisthotonos
Sialorrhea
Trismus

Autonomic dysfunction (2 or more)*

Hypertension (diastolic blood pressure at least 20 mm Hg above baseline)
Incontinence
Prominent diaphoresis
Tachycardia (heart rate at least 30 bpm above baseline)
Tachypnea (respiration > 25 breaths/min)

*The required number of signs/symptoms from each of the 3 categories must be present before a diagnosis of neuroleptic malignant syndrome can be made; if signs and symptoms from 1 of the 3 categories cannot be documented, then the required number from 2 of the categories must clearly be present, plus 1 of the following findings: (1) clouded consciousness (eg, delirium, mutism, stupor, coma); (2) leukocytosis (leukocyte count > 15 × 10^3/mm^3; (3) creatine kinase level > 1000 U/L.

Data from Levenson[13] and Pope et al.[30]

Dopamine agonists such as bromocriptine and amantadine have been shown to be effective in the management of NMS and to shorten the course of illness. Bromocriptine directly activates postsynaptic receptors and offsets the central inhibition of dopamine.[2,4] It also stimulates production of dopamine from the pituitary gland to reverse the hyperthermic responses resulting from dopamine blockade. Amantadine functions through a presynaptic mechanism to counteract neuroleptic dopaminergic inhibition, with similar end results. Consequently, treatment with dopamine agonists should be continued until there is clear resolution of symptoms.

Dantrolene can be used in cases of fulminant NMS

Table 4. Guidelines for Treating Neuroleptic Malignant Syndrome

Discontinuation of the offending neuroleptic agent
Airway management (early intubation for airway protection, adequate oxygenation and ventilation, continuous pulse oximetry)
Circulatory support (continuous cardiac monitoring, fluid resuscitation, hemodynamic support)
Cooling measures (evaporative measures [eg, fan, mist], cooling blankets, application of ice packs, antipyretic therapy)
Screening for infections (via computed tomography scans of the head, chest radiography, analysis of cerebrospinal fluid obtained on lumbar puncture, blood and urine cultures)
Toxicology screen
Transfer to critical care
Administration of pharmacologic agents
Amantadine (for hyperthermia): 100 mg orally twice daily
Bromocriptine (for hyperthermia): 5 mg dose initially, then 2.5–10 mg orally or nasogastrically 3 times daily as required
Dantrolene (for hyperthermia and muscular rigidity): 2–3 mg/kg body weight intravenously every 6 h (to a maximum of 10 mg/kg per 24 h)
Benzodiazepines (for muscular rigidity)
Avoidance of anticholinergic agents

to help control both muscle rigidity and hyperthermia.[2,4,6] Dantrolene is a direct muscle relaxant that works by blocking the release of calcium from the sarcoplasmic reticulum, thus working in tandem with the effects of central dopamine agonists to counteract the peripheral pyrexic mechanisms of NMS. Dantrolene was initially used in the treatment of malignant hyperthermia (MH), a hereditary muscle disorder related to the use of inhalational anesthetic agents or depolarizing muscle relaxants. Whereas the clinical manifestations of MH parallel those of NMS, the underlying mechanism of MH is thought to result from a genetic defect of calcium transport at the skeletal muscle level.[6,7,9,31]

Additional pharmacologic agents used in cases of NMS include benzodiazepines, which exert a central muscle relaxant effect and may work synergistically with dopaminergic agonists to attenuate muscle-generated heat in NMS. Conversely, anticholinergic medications have no defined role in the management of NMS and may in fact worsen the course of disease.[6]

REINSTITUTING NEUROLEPTIC THERAPY

The issue of reinstituting neuroleptic treatment for an underlying psychotic disorder following full recovery from an episode of NMS remains vexing. Alternative therapies for the psychotic disorder would be preferable. However, if management of a psychotic disorder demands further use of neuroleptic drugs, certain modifications in therapy can result in decreased risk for NMS recurrence.[2] A 2-week minimum washout period should elapse between the time from full resolution of NMS and return to dopamine antagonist therapy.[2,7] Reduction of risk factors for NMS should also be attempted before such therapy is reinstituted. Concomitant medical illness requires optimal management, and dehydration requires correction. Symptoms of agitation may be better controlled with low-dose benzodiazepines. Resumption of therapy should begin under informed consent and close clinical scrutiny with low-dose and low-potency agents, followed by a slow, cautious upward titration to full effectiveness.[7] The patient should be closely monitored—initially in an inpatient setting—for any early signs of NMS; if such signs appear, prompt treatment for NMS should begin again, including withdrawal of further neuroleptic treatment.

SUMMARY

NMS is a relatively uncommon but potentially lethal idiosyncratic disorder related to the use of neuroleptic medications. It may occur at any time during treatment with dopamine antagonists and affects patients in all age groups. Some patients are more susceptible to NMS than are others. The cardinal features of this disorder are nonspecific and include muscular rigidity, altered sensorium, autonomic instability, and hyperthermia. The diagnosis of NMS is made by exclusion in the appropriate clinical setting. Laboratory evaluation should be focused on excluding other possible and more common entities with similar manifestations. Treatment begins with early recognition of the syndrome and immediate withdrawal of the offending agent, followed by supportive care and specific pharmacologic therapies. **HP**

NOTE

The views expressed in this article are those of the author and do not reflect the views of the US government, the Department of Defense, or the US Navy.

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