Neuroleptic Malignant Syndrome

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Introduction

Neuroleptic malignant syndrome (NMS) is a rare and potentially life-threatening drug-induced neurologic emergency characterized by fever, muscle rigidity, altered mental status, and autonomic dysfunction [1]. NMS is believed to be a result of dopamine deficiency from excessive dopaminergic blockade by antipsychotic medication and several anti-emetics, and less often by withdrawal of dopamine agonist therapy [2, 3]. Successful treatment requires prompt recognition, cessation of offending agents, aggressive supportive care, and administration of certain pharmacotherapies and interventions, such as dantrolene, bromocriptine and electroconvulsive therapy (ECT). While NMS is easily recognized in its severe form, early identification can be challenging because it is heterogeneous in onset and progression and several medical conditions exhibit similar symptoms [4–8]. The variability in NMS presentation makes controlled trials and collection of data difficult, and consequently, many aspects remain controversial, including pathophysiological mechanisms, risk factors, diagnostic criteria, prognosis and treatment [9].

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Case Presentation

An 87-year-old man with atrial fibrillation on rivaroxaban (Xarelto) and mild dementia was admitted from the medical-behavioral unit (MBU) to the intensive care unit (ICU) with hypoxemia, fever and muscle rigidity. Six days prior, he presented to the emergency department (ED) with a scalp hematoma after an unwitnessed fall at home. Physical exam in the ED was otherwise normal and computed tomography (CT) scans of his head and cervical spine were negative for acute injury or pathological process. An episode of agitation in the ED was treated a 5 mg intramuscular (IM) injection of haloperidol and the patient was admitted for observation. Of note, the patient's wife reported an acceleration in his dementia over the past few months and he was recently made DNR/DNI; he has been increasingly confused, with episodes of agitated behavior mostly at night, with restless legs while sleeping and periodic falls out of bed. The day after admission, the patient was appropriate and cooperative but in the evening, he became acutely agitated, confused and combative, grabbing and hitting staff. He ripped out his intravenous catheter and haloperidol, 3 mg, was again administered intramuscularly. The following day, the patient was admitted to the MBU under the care of a geriatric psychiatrist. He exhibited impulsive behavior and confusion with periods of restlessness and fidgety movements. At times, he was combative, requiring quetiapine (Seroquel) 12.5 mg every 6 h and olanzapine

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(Zyprexa) 1.25 mg IM daily over the course of three days. On the morning of the sixth day after his fall, the patient was noted to have poor appetite and was less interactive than previously. He appeared withdrawn and was not responding to verbal cues over the course of the day. In the afternoon he was noted to have increasing tremor in his arms and legs and diffuse muscle rigidity with new-onset coughing spasms. His blood pressure (BP) was 122/95 but his previously rate-controlled atrial fibrillation was now 171 beats per minute (bpm). His respirations at 20 breaths per minute were associated with a gurgling noise and his oxygen (O_2) saturation was 86 % on room air. His axillary temperature was 98.9 °F. Repeat vital signs on 2 l per minute of O_2 by nasal cannula improved saturation to 90–92 %, but BP had decreased to 82/33, and his temperature measured rectally was 103.2 °F. The patient was placed on a non-rebreather (NRB) face mask and transferred to the ICU. In the ICU, the patient was nonverbal, febrile to 104.1 °F and displayed lead-pipe rigidity. He remained with an O_2 saturation above 95 % on NRB. Repeat CT head showed no new bleed or other intracranial process. A cooling blanket and ice packs were applied and 4 l of normal saline were given for hypotension and decreased urine output. Laboratory studies were remarkable for a white blood cell count of 9.2×10^3 μL, with 90 % neutrophils and creatine kinase (CK) level of 1273 U/L (Normal, 35–232 U/L). Urinalysis, electrolytes, thyroid function tests, liver enzymes and coagulation studies were normal. A lumbar puncture was performed with a normal CSF profile and all cultures and serologies were negative. EEG was within broad limits of normal.

Question How do you make this diagnosis?

Answer By exclusion. Neuroleptic Malignant Syndrome is diagnosed by eliminating other potential causal explanations for the typical clinical findings

After the exclusion of CNS infection, cerebrovascular abnormality, status epilepticus, and systemic conditions, a diagnosis of neuroleptic malignant syndrome (NMS) was made based on altered mental status, muscle rigidity, hyperthermia, hemodynamic instability and elevated creatine kinase in the setting of recent exposure to haloperidol, quetiapine and olanzapine. All antipsychotics were stopped. Benzodiazepines were considered to control the rigidity but were avoided given concerns for respiratory failure in this DNI patient. A nasogastric tube was inserted and the patient was given bromocriptine 2.5 mg every six hours. Strict volume status assessments and serial electrolyte and renal function laboratory testing were performed to guide IV hydration for a goal of euvolemia. Heart rate improved to the low 90s with fluid administration. Piperacillin/tazobactam was given for 3 days but was stopped once cultures were finalized. After four doses, bromocriptine was increased to 5 mg every 6 h. The patient's symptoms slowly improved over the following week, with rigidity, hyperthermia and autonomic dysfunction resolving before his mental status returned to baseline.

Principles of Management

Diagnosis

In 2011, an international multispecialty expert panel published consensus recommendations for diagnostic criteria of NMS using a set of quantitative critical values and priority-scored clinical features [10]. While this criteria system has yet to be independently validated, it may help guide diagnosis. Clinical features were given a priority score by the panel for their relative importance in contributing to the diagnosis. The following features are listed in order of higher to lower scored values: recent dopamine antagonist exposure, or dopamine agonist withdrawal; hyperthermia; rigidity; mental status alteration; CK elevation; sympathetic nervous system lability; tachycardia plus tachypnea; and a negative work-up for other causes. The critical values were defined as hyperthermia > 100.4 °F or > 38.0 °C on at least 2 occasions, CK level at least 4 times the upper limit of normal, blood pressure elevation of ≥ 25 % above baseline, blood pressure fluctuation ≥ 20 mmHg diastolic

or ≥ 25 mmHg systolic change within 24 h; tachycardia ≥ 25 % above baseline, and tachypnea ≥ 50 % above baseline.

This distinct set of clinical features and laboratory abnormalities are all highly associated with NMS yet no single test is specific to the diagnosis. A workup to rule out other serious neurological or medical conditions, including central nervous system (CNS) infections, toxic or metabolic etiologies, inflammatory or autoimmune conditions, status epilepticus and systemic conditions is an essential first step. The diagnosis of NMS is subsequently made based on positive clinical and laboratory findings after the exclusion of alternative causes [10]. In a clinical review of 153 published case reports of NMS, mental status change or muscle rigidity was the initial manifestation in 82.3 % of cases [11]. These early symptoms should prompt brain imaging studies and lumbar puncture to exclude intracranial pathology such as subarachnoid hemorrhage (SAH) and CNS infection [12], and electroencephalography can rule out status epilepticus. However, it may be difficult to distinguish NMS from other medication-induced movement disorders, toxin-induced hyperthermias and acute dysautonomias such as serotonin syndrome (SS), malignant hyperthermia (MH), malignant catatonia, and central anticholinergic syndrome (CAS).

Medication History and Temporal Clues

The patient's medication history along with the temporal progression of signs and symptoms provide the most valuable clues to diagnosis (Table 39.1). Most cases of NMS present gradually within the first week of drug administration, and all usually within 30 days [13]. In contrast, malignant hyperthermia, anticholinergic syndrome and serotonin toxicity tend to present rapidly after exposure to causative agents [14, 15]. Nearly all dopamine antagonists have been implicated in NMS. Withdrawal of dopamine agonists has also been associated with a less severe form. Conventional, "typical," or first-generation antipsychotic (FGA) agents pose greater risk than newer "atypical" or second-generation antipsychotic (SGA) drugs and certain antiemetic medications [6, 16–22]. NMS occurs within the therapeutic dosage range of antipsychotics and is not a dose-dependent phenomenon. Though recent or rapid dose escalation, higher doses, parenteral administration and a switch from one agent to another have been implicated as risk factors in case–control studies [5, 23–27]. Additional factors associated with a heightened risk of neuroleptic malignant syndrome include exhaustion, dehydration, and iron deficiency [24, 27, 28].

Drugs with anticholinergic activity, such as tricyclic antidepressants, antihistamines, phenothiazines, and antiparkinson agents can cause fever by disturbing central hypothalamic function and decreasing peripheral heat dissipation [29–32]. Marked hyperthermia and CAS can occur when these drugs are taken in combination. Anticholinergic medications are a common treatment for FGA extrapyramidal side effects; distinguishing between NMS and CAS by medication history can be difficult in these patients. Direct or indirect serotonin agonists lead to SS and diagnosis of NMS may be also be challenging in patients taking both serotonergic and neuroleptic agents [33]. On the other hand, exposure history is helpful in distinguishing between NMS and MH, a hypermetabolic crisis that occurs when a MH-susceptible individual is administered potent halogenated inhalational anesthetics or succinylcholine. When the history uncovers several possible offending drugs from multiple categories or in the absence of a reliable history, a detailed examination of clinical features can also be useful in differentiating among disorders [34] (Table 39.1).

The Clinical Tetrad of NMS: Clues to Diagnosis and Management Concerns

A review of 222 published cases revealed a common sequence of symptom development in 70.5 % of NMS patients, beginning with mental status changes, followed by muscle rigidity, then

Table 39.1 Differential diagnosis for neuroleptic malignant syndrome

		Disorder	Onset time	Muscular symptom	Other features	Postulated mechanism	Causative agents	Possible treatments
Medication-induced movement disorder		Medication-induced acute dystonia	Hours to a few days	Sustained, involuntary muscle contraction, torticollis, retrocollis, oculogyric crisis, blepharospasm	–	Imbalance of dopaminergic/cholinergic transmission	Neuroleptic dosage increase or decrease in dosage of medication to treat EPS	Anticholinergics, benzodiazepines
		Medication-induced acute akathisia	Hours to days	Fidgety movements of the legs, rocking from foot to foot, pacing	Complaints of restlessness and unease	Mesocortical D_2 antagonism		Dose reduction, propranolol, benzodiazepines, anticholinergics
		Neuroleptic-induced parkinsonims	Weeks	Akinesia, bradykinesia, rigidity, shuffling gait, resting tremor	Masklike facies, postural instability	Postsynaptic striatal D_2 antagonism		Dose reduction, anticholinergics, dopamine agonists
		Tardive dyskinesia	3 months to years	Late onset involuntary athetoid or choreiform movements, buccolinguomasticatory movements	–	Excess dopaminergic activity	Neuroleptic use for at least a few months	Early recognition, stop offending antipsychotic, cholinergics
	Toxin-induced hyperthermia	Neuroleptic malignant syndrome	2–10 days	Lead-pipe rigidity, bradyreflexia	Altered mental status, hyperthermia, autonomic instability, catatonia, mutism	D_2 antagonism in striatum, hypothalamus and mesocortex	FGAs (chlorpromazine, haloperidol, fluphenazine), SGAs (clozapine, risperidone, olanzapine, quetiapine), antiemetics (prochlorperazine, promethazine, trimethobenzamide, thiethylperazine, metoclopramide), amoxapine	Early recognition, stop offending drug, cooling, fluid resuscitation, cardiopulmonary support, benzodiazepines, dantrolene, bromocriptine, amantadine, or other direct-acting dopamine agonist, ECT

(continued)

		Disorder	Onset time	Muscular symptom	Other features	Postulated mechanism	Causative agents	Possible treatments
		Serotonin syndrome	Hours (<24)	Clonus, hyperreflexia, fasciculation, tremor	Anxiety, disorientation, psychomotor agitation, hyperalertness, hyperthermia, autonomic hyperactivity, gastrointestinal symptoms	Excessive stimulation of serotoninergic receptors in the peripheral and central nervous system	MAOIs, SSRIs, meperidine, dextromethorphan, TCAs, L-tryptophan, lithium, linezolid, valproate, ondansetron	Cyproheptadine, active cooling
		Central anticholinergic syndrome	1 to 2 h	Myoclonus, choreoathetosis	Hypervigilance, agitation, hallucinations, delirium, coma, mydriasis, hyperthermia, tachycardia, hypertension, tachypnea, dry flushed skin, dry mucous membranes, decreased bowel sounds, urinary retention	Central cortical and subcortical muscarinic receptor antagonism	Antihistamines, TCAs, cyclobenzaprine, orphenadrine, antiparkinson agents, antispasmodics, phenothiazines, atropine, scopolamine	Physostigmine, supportive care
		Malinant hyperthermia	Minutes to hours (<12 h)	Rigor mortis-like rigidity	Hypercarbia, tachycardia, tachypnea, mixed respiratory and metabolic acidemia, hyperthermia, rhabdomyolysis	AD gene disorder of ryanodine receptor Ca^{+} channel, uncontrolled release of Ca^{+} with elevation of intracytyoplasmic Ca+ levels, continuous muscle activation, and ATP breakdown. SR Ca^{+} pump unable to re-sequester Ca^{+}. ATP breakdown further aggravates heat production	Volatile anesthetic agents (halothane, isoflurane, sevoflurane, desflurane), depolarizing neuromuscular blocker (succinylcholine)	Dantrolene, active cooling

D_2 dopamine type-2 receptor, *AD* autosomal dominant, *Ca^{+}* calcium, *SR* sarcoplasmic reticulum, *ATP* adenosine triphosphate, *EPS* extrapyramidal signs, *FGA* first-generation antipsychotic, *SGA* second-generation antipsychotic, *MAOI* monoamine oxidase inhibitor, *SSRI* selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressant, *ECT* electro-convulsive therapy

hyperthermia, and finally autonomic dysfunction [11]. Appearance of any of these four cardinal signs should prompt early initiation of supportive care with a low threshold for suspicion since NMS complications are severe and occur frequently. A recent analysis of the nationwide inpatient sample (NIS) database was performed, identifying rates of complications, mortality, and outcomes in 1346 patients with NMS from 2002 to 2011 [35]. In-hospital death occurred in 75 (5.6%) patients and the most prevalent complication was rhabdomyolysis (30.1%). Universal management of NMS includes immediate discontinuation of the offending drug, or reinstitution in the case of abrupt discontinuation of dopaminergic therapy, correction of dehydration and electrolyte imbalance, controlling the hyperthermia and rigidity, and preventing complications. The need for monitoring in an intensive care unit with expert and robust supportive care is undisputed.

Hyperthermia

Abrupt reduction in dopaminergic transmission in the hypothalamus alters the core temperature set point, leading to impaired thermoregulation in NMS [36]. Blockade of dopamine receptors in the corpus striatum causes muscular rigidity and secondary heat production. While fever is a defining symptom in NMS, many conditions in critically ill patients result in inflammation, tissue injury and a febrile reaction and it may be difficult to determine the etiology of a fever early in the clinical course. Leukocytosis, ranging from 10,000 to 40,000/μL, with or without a "left shift" is a consistent laboratory finding in NMS [37]. Obtaining appropriate cultures should not be avoided although approximately half of febrile patients in the intensive care unit (ICU) will have a non-infectious cause of fever, with most no greater than 38.9 °C (102 °F) [38]. A fever in excess of 38.9 °C (102 °F) is usually of an infectious etiology, though a transfusion reaction or a drug fever may also trigger temperatures exceeding 102 °F [39]. In patients with a temperature greater than 104 °F, however, NMS, SS, MH and SAH should always be considered. Hyperthermia should be aggressively treated with cooling blankets, ice packs and fans. The role of NSAIDs and acetaminophen in toxin-induced hyperthermia is not established but antipyretic agents can be helpful if an infection is a comorbid factor.

Altered Mental Status

A reduced or fluctuating level of consciousness typically precedes systemic signs in patients with NMS [11] but the onset of symptoms may be underappreciated given the psychiatric comorbidity of susceptible patients. Altered mental status is multifactorial and may reflect hypothalamic and spinal dopamine receptor antagonism, hyperthermia effects on the CNS, or direct effects of other drugs [40]. Individuals may appear alert but dazed and unresponsive. Catatonic signs and mutism can be prominent and patients may evolve into profound encephalopathy and eventual coma [41]. Malignant or lethal catatonia, a condition similar to NMS that some argue is on the same spectrum [42], can be distinguished by a several-week prodrome of psychosis, agitation, and catatonic excitement [43, 44]. Hyperactivity and agitation are common to SS and CAS, in contrast to the catatonic stupor more prevalent in NMS [12].

Muscular Rigidity

Interference with nigrostriatal dopamine pathways contributes to muscle rigidity and tremor in NMS, classically characterized by "lead pipe rigidity" or stable resistance through all ranges of motion when passively moving the extremities [1, 2, 45, 46]. The motor symptoms of malignant catatonia display more positive phenomena (dystonic posturing and stereotyped repetitive movements) than what is seen in NMS while the presence of myoclonus, ataxia, shivering and hyperreflexia is more indicative of serotonin syndrome [33, 47] (Table 39.1). Patients with anticholinergic syndrome have few muscular abnormalities because skeletal muscle contraction is effected by nicotinic rather than muscarinic transmission. The muscle rigidity seen in malignant hyperthermia, however, is quite similar to

NMS and must be distinguished by the clinical setting. Tremor is often associated with NMS, and dystonia, trismus, chorea, opisthotonus, and other dyskinesias are present less commonly [5, 48]. Patients can also have prominent dysarthria, sialorrhea, and dysphagia and prophylactic intubation may be required. Acute respiratory failure was the strongest independent predictor of mortality ($p<0.001$) in the NIS database analysis [35]. Creatine kinase concentration may be elevated before the onset of muscle rigidity and higher levels are consistent with a poor prognosis [48–50]. Muscle damage and necrosis from the metabolic inequality between energy consumption and production can progress quickly to rhabdomyolysis, with associated hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia and lactemia. Aggressive fluid resuscitation to maintain adequate urine output is imperative in preventing progression to acute myoglobinuric renal failure, compartment syndrome, cardiac dysrhythmias from electrolyte abnormalities, and disseminated intravascular coagulopathy [51, 52]. Sodium bicarbonate to alkalinize the urine and prevent breakdown of myoglobin into nephrotoxic metabolites is often used though it has not been shown to be superior to saline alone, and bicarbonate may worsen hypocalcemia [51].

Autonomic Dysfunction

Dysautonomia in NMS is likely due to hypothalamic dopamine type-2 (D_2) receptor blockade. Removal of normal dopamine regulation of efferent sympathetic activity leads to autonomic activation while unregulated vasomotor and sudomotor activity causes labile blood pressure and heart rate [53]. Early clues of autonomic instability are urinary incontinence, pallor and profuse diaphoresis, with increased "insensible fluid losses." Hypotension should be treated with generous isotonic crystalloid administration but vasopressors, antiarrhythmic agents or pacing may be required. Respiratory distress and tachypnea are common and result from hypermetabolism and subsequent metabolic acidosis. Chest wall restriction, autonomic dysfunction with loss of protective airway reflexes and aspiration pneumonia can lead to respiratory failure.

Evidence Contour

Treatment of NMS with pharmacological agents and electroconvulsive therapy (ECT) is controversial and large clinical trials investigating specific therapies are lacking. Recommendations for the use of single- or combination-therapy consisting of benzodiazepines, dantrolene, bromocriptine, amantadine and ECT are based upon case reports and anecdotal evidence and their benefit over good supportive care is debated [54, 55]. The lack of other proven treatments and high fatality rate of the disorder easily justifies their use in patients with severe NMS.

Benzodiazepines

Benzodiazepines are the most widely used pharmacologic adjuncts in management of NMS because of their rapid onset of action and usefulness in reversing catatonic symptoms and agitation. Benzodiazepines facilitate GABA-mediated chloride transport, producing neuronal hyperpolarization which attenuates the sympathetic hyperactivity characterized by NMS [40]. Several clinical reports suggest that lorazepam and other benzodiazepines may reduce recovery time and improve outcome [19, 56, 57] and a few cases found benzodiazepines to be effective when other medications failed [58]. A trial of lorazepam, starting with 1–2 mg parenterally, is a reasonable first-line intervention for acute NMS with difficulty in assessing mental status as the primary disadvantage.

Dantrolene

Because of its efficacy in reducing heat production, rigidity and oxygen consumption in anesthetic-induced malignant hyperthermia, dan-

trolene, a direct-acting skeletal muscle relaxant, has been used in the treatment of NMS. Dantrolene is believed to decrease skeletal muscle contraction by interfering with calcium ion release from the sarcoplasmic reticulum which uncouples the excitation-contraction process. In some meta-analyses, improvement of NMS occurred in approximately 80 % of patients treated with dantrolene monotherapy [59–61]. In contrast, a more recent meta-analysis of 271 published cases found that treatment of NMS with dantrolene as monotherapy was associated with a higher mortality, and complete time to remission was prolonged by combination therapy including dantrolene [54]. Dantrolene can be administered intravenously starting with an initial bolus dose of 1–2.5 mg/kg followed by 1 mg/kg every 6 h up to a maximum dose of 10 mg/kg/day [6, 60–63]. Effects are usually reported within minutes of administration. Due to a risk of hepatoxicity, dantrolene is typically discontinued once symptoms begin to resolve although some recommend continuing for 10 days followed by a slow taper with doses of oral dantrolene that range from 50 to 200 mg/d to minimize relapse [63].

Bromocriptine

Bromocriptine is a centrally acting synthetic dopamine agonist that stimulates D_2 receptors and antagonizes type-1 receptors (D_1) in the hypothalamus and the neostriatum of the CNS. Bromocriptine is used in NMS to reverse the hypodopaminergic state precipitated by the antipsychotic-related striatal D_2 antagonism and therefore ameliorate the manifestations of NMS [2]. In a review of 67 published cases of NMS, Bromocriptine was found to significantly shorten time to clinical response compared to supportive treatment alone [60] and a larger review of 734 cases found that bromocriptine significantly reduced mortality rate compared with supportive care (10 % versus 21 %) [61]. In contrast, a small prospective study in 20 patients showed that dantrolene and/or bromocriptine use was associated with a more prolonged course (9.9 versus 6.8 days) and a higher incidence of complications compared with those receiving supportive care alone [55]. However, patients in the treated group of this nonrandomized study were sicker than those not treated. Bromocriptine is not available in an injectable form and therefore, can be given only orally or through a feeding tube, starting with doses of 2.5 mg, 2–3 times daily, increasing doses by 2.5 mg every 24 h until a response is obtained or until reaching a maximum dose of 45 mg/day. It is recommended that bromocriptine be continued for 10 days after symptoms are controlled and then tapered slowly to minimize the likelihood of recrudescence of NMS [6, 60, 61, 63].

Amantadine

Other dopamine agonists with anecdotal evidence of success include ropinirole, levodopa [64, 65], and amantadine [6, 66, 67]. Dopaminergic agents may be associated with exacerbation of underlying psychiatric illness but is usually well tolerated in psychotic patients. Amantadine has been used to treat Parkinson disease and has been tried in neuroleptic malignant syndrome because it increases synaptic dopamine activity. Its antiparkinsonian activity results from blocking reuptake of dopamine into presynaptic neurons and causing direct stimulation of postsynaptic receptors.

Electroconvulsive Therapy

Although there are no prospective, randomized, controlled data, the efficacy of ECT in treating malignant catatonia and improving Parkinsonism provide rationale for its use in NMS, especially in patients not responding to other treatments or in whom non-pharmacologic psychotropic treatment is needed. Clinical response, presumably by enhancing central dopaminergic transmission, was seen by the third or fourth treatment in a review of 5 patients treated with ECT, and after an average of 4.1 treatments in a comprehensive literature review of 55 patients [68, 69]. A review

of published cases found a lower mortality rate in ECT treated patients compared with those receiving supportive care alone [70]. The interpretation of these results are limited by variable timing of ECT in relation to symptom onset and lack of randomization.

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