Early detection of an atypical presentation of neuroleptic malignant syndrome: A case report

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Abstract

Neuroleptic malignant syndrome (NMS), which is considered a neurologic emergency, is believed to be caused by exposure to dopamine antagonist or withdrawal from a dopamine agonist. This article reports a case of suspected atypical NMS in a patient following rapid conversion of ziprasidone to risperidone without titration. While the initial presentation did not fully meet the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, diagnostic features, a sequential treatment strategy was initiated and the patient appropriately responded to antipsychotic cessation in addition to combination therapy with dantrolene and bromocriptine. Neuroleptic malignant syndrome diagnostic criteria, treatment, and prognosis are discussed.

Keywords: neuroleptic malignant syndrome, NMS, catatonia, antipsychotic, ziprasidone, risperidone, fluoxetine, bromocriptine, dantrolene

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an increased risk of developing NMS include dehydration, iron deficiency, agitation, exhaustion, and any prior episode of NMS.¹ While the precise mechanism remains unknown, reduced dopaminergic activity is believed to be central to disease etiology. The hypothalamus, nigrostriatal dopamine tract, and dysfunction of the frontal lobe lead to core symptoms of NMS.⁵

Background

Neuroleptic malignant syndrome (NMS) is an idiopathic, life-threatening complication that can occur in individuals exposed to a dopamine antagonist.¹ The syndrome is characterized by 4 common symptoms: altered mental status, muscle rigidity, pyrexia, and autonomic dysfunction.² It reportedly affects 0.01% to 0.02% of patients treated with an antipsychotic medication,¹ and first-generation antipsychotics are more commonly implicated compared with second-generation antipsychotics (SGAs). Case-control studies^{3,4} have demonstrated an increased risk of NMS with parenteral administration, rapid titration, and higher drug dosages. Clinical factors associated with

Patient Case Report

A 40-year-old woman with a history of schizophrenia presented to the emergency department via the help of a caregiver. The caregiver voiced the patient's complaints of weakness and difficulty walking. The patient was stiff, was unable to move, was not responsive to staff, and appeared confused. Nineteen days before the emergency department presentation the patient had a psychiatric admission totaling 13 days related to visual and auditory hallucinations, delusions, and paranoia. Prior to this initial visit, the patient was receiving no psychotropic medications and was able to talk and respond to questions. Past medical history was positive for type 2 diabetes mellitus (controlled with sliding scale insulin aspart), scoliosis, gastro-

esophageal reflux disease, and borderline intellectual functioning. While hospitalized, the patient began treatment with citalopram 20 mg daily and risperidone 1 mg at bedtime. The patient refused medications, so intramuscular (IM) ziprasidone 20 mg twice daily along with lorazepam 0.5 mg IM 3 times daily as needed were ordered on hospital day 3. Ziprasidone and lorazepam injections were administered for 8 days. With gradual improvement in clinical symptoms (the patient began eating, denying hallucinations, and demonstrating less paranoia by coming out of her room and agreeing to take medications), a change to oral dosing was warranted and pursued by the psychiatrist. Two days prior to discharge, lorazepam was changed to 0.5 mg by mouth 3 times daily as needed, and ziprasidone 20 mg IM twice daily was changed to risperidone 6 mg by mouth at bedtime. The psychiatrist selected risperidone because the insurance company considered ziprasidone a nonpreferred agent, so there were copay concerns. The patient received 2 doses of the risperidone 6 mg at bedtime prior to discharge to an assisted-living facility. The discharge diagnosis was schizophrenia with catatonic features. Discharge psychiatric medications included fluoxetine 20 mg daily, lorazepam 0.5 mg 3 times daily as needed, and risperidone 6 mg at bedtime (compliance reported by the facility). Documentation of the reasoning for changing citalopram to fluoxetine was not provided in the hospital discharge summary. The patient's presentation to the emergency department occurred 5 days after discharge from this hospitalization.

During workup, the patient's condition worsened and required admission to the intensive care unit. At this time the patient displayed symptoms of muscular rigidity and autonomic instability (hypertension and tachycardia) without hyperthermia, diaphoresis, or incontinence. Vitals and laboratory data on presentation included blood pressure 160/105 mmHg, heart rate 107 beats/min, respiratory rate 20 breaths/min, $T_{\max}$ 98.5°F, serum creatinine 0.55 mg/dL, creatine kinase (CK) 536 U/L, thyroid-stimulating hormone 0.61 mU/L, white blood cell count $7.4 \times 10^9/L$, and troponin <0.01 ng/mL. The patient received diphenhydramine and lorazepam without improvement and with noted sedation. While in the intensive care unit, empiric NMS treatment was initiated, which included cessation of risperidone and eventual initiation of dantrolene 75 mg per nasogastric tube (NGT) every 6 hours and bromocriptine 2.5 mg per NGT every 6 hours. Computed tomography yielded unremarkable results, as did the toxicology screen. No electroencephalogram or lumbar puncture was preformed due to high suspicion of NMS. Electrocardiogram testing revealed sinus tachycardia and early repolarization, which were resolved by treatment day 2. The patient remained afebrile. Signs of altered mental status, muscular rigidity, and autonomic dysfunction gradually improved through-

out treatment. Dantrolene and bromocriptine were continued throughout hospitalization and tapered to discontinuation over a total of 8 days. Dantrolene was decreased to 50 mg per NGT every 6 hours on day 3, to 25 mg per NGT every 6 hours on day 5, and to 25 mg orally every 8 hours on day 7; one last dose of dantrolene was given on day 8. Bromocriptine was tapered to 2.5 mg NGT every 12 hours on day 3, then on day 8, the patient received bromocriptine 2.5 mg orally once. The NGT was removed on day 6, and the patient resumed oral medications at that time. Once the patient stabilized she was discharged to a rehabilitation facility and had a complete recovery from the NMS episode. Approximately 2 months following discharge, the patient returned for a nonpsychiatric admission. Of note, ziprasidone 20 mg at bedtime had been initiated by her outpatient provider. It is unclear when exactly resumption of antipsychotic treatment occurred; however, the patient had been tolerating therapy without incident.

Literature Review

According to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5),¹ a diagnosis of NMS can be considered in a patient with exposure to a dopamine antagonist in the presence of severe muscle rigidity, hyperthermia, and autonomic dysfunction (diaphoresis, dysphagia, tremor, urinary incontinence, changes in consciousness, mutism, tachycardia, labile blood pressure, leukocytosis, and laboratory evidence of muscle injury via elevated creatinine kinase levels). Atypical presentation may include onset without muscle rigidity or hyperthermia. These symptoms may be milder, may develop over time, or may not develop at all. Patients may also have fewer extrapyramidal symptoms and smaller increases in CK. This type of presentation is more common with SGAs and may be seen in patients who present for care early in the onset.⁶ Onset usually occurs soon after initiation of an antipsychotic or after a dose titration, and it is uncommon past 1 month of treatment.⁶ Controversy remains over whether or not NMS should be considered a spectrum disorder, as various presentations in symptom type, timing, and severity exist. Clinical presentation can range from severe rigidity, renal dysfunction, autonomic instability, and elevated CK levels to confusion with only minimal laboratory and autonomic changes.⁷

Although many consider the DSM-5 to be the current gold standard for psychiatric and related disorders, other diagnostic criteria for NMS exist, including the Levenson criteria, the Nierenberg criteria, and the Delphi method (Table 1). Overall, these criteria have many similarities. All criteria address the recent use or exposure to a dopamine antagonist; however, only the Nierenberg criteria and Delphi method consider withdrawal from a dopamine

TABLE 1: Diagnostic criteria comparison⁸⁻¹⁰

Levenson	Nierenberg	Delphi Method ^a	Priority Score
Essential Recent antipsychotic use	Essential • Recent antipsychotic or dopaminergic use • Dopamine agonist discontinuation	Exposure to dopamine antagonist <i>or</i> dopamine agonist withdrawal within preceding 72 h	20
		Hyperthermia >100.4°F (38.0°C) on ≥2 occasions, measured oral	18
Major • CK >1000 IU/L • Fever • Muscle rigidity	Major • Fever (>100.4°F) • Muscle rigidity (lead pipe) • CK ≥3× ULN • Autonomic instability (>2 of the following: altered consciousness, diaphoresis, hypertension/hypotension, tachycardia)	Rigidity	17
		Mental status alteration (↓ <i>or</i> fluctuating consciousness)	13
Minor • AMS • Abnormal BP • Diaphoresis • Leukocytosis • Tachypnea • Tachycardia	Minor • Autonomic instability (1 criteria, including those listed above, plus incontinence or arrhythmia) • Respiratory distress (tachypnea, hypoxia, respiratory failure) • EPSs • Leukocytosis	↑ CK (>4× ULN)	10
		SNS lability, defined as ≥2 of the following: • BP elevation (SBP or DBP >25% above baseline) • BP fluctuation (ΔSBP ≥25% or ΔDBP ≥20%) • Diaphoresis • Urinary incontinence	10
Required • Essential <i>and</i> • 3 Major <i>or</i> • 2 Major <i>and</i> 4 minor	Required • Essential <i>and</i> • 4 Major <i>or</i> • 3 Major <i>and</i> 3 minor	Hypermetabolism, defined as: • ↑ HR (≥25% above baseline) <i>and</i> • ↑ RR (≥50% above baseline)	5
		Negative workup for other causes: Infectious, toxic, metabolic, or neurologic	7

AMS = altered mental status; BP = blood pressure; CK = creatine kinase; DBP = diastolic blood pressure; EPS = extrapyramidal symptom; HR = heart rate; RR = respiratory rate; SBP = systolic blood pressure; SNS = sympathetic nervous system; ULN = upper limit of normal.

^aThe Delphi method score description is available in the Literature Review section.

agonist as a precipitating cause.^{8,9} Both the Levenson and Nierenberg criteria have required major and/or minor features essential for diagnosis, whereas the Delphi Method has a point-value system assigned to different clinical symptoms of NMS. Patients may achieve a Delphi score from 0 to 100 based on symptomatic presentation. There is no definitive point value diagnostic of NMS. Rather, as the point value increases, so does the likelihood of NMS.

Given the overlap in presentation of NMS with other disease states and drug-induced syndromes, the differential diagnosis should include related conditions. Serotonin syndrome is a non-idiopathic drug response characterized by excessive serotonergic activity within the central nervous system. Presentation overlaps with NMS given the occurrence of autonomic instability and altered mental status, but gastrointestinal distress and hyperreflexia are distinguishing features of serotonin syndrome and not NMS.¹¹ Malignant catatonia, like NMS, is a life-threatening neurologic emergency characterized by hyperthermia, autonomic dysfunction, and muscular rigidity. The similarity in clinical features makes differentiation

between the 2 syndromes challenging. Diagnostic distinction is reliant upon medication exposure as symptomatic occurrence in the absence of antidopaminergic therapy is indicative of malignant catatonia.¹²

Treatment

Due to associated morbidity and mortality, immediate cessation of the suspected causative agent(s) is recommended. In the setting of suspected NMS due to dopamine agonist withdrawal, prompt resumption of therapy is prudent. Supportive care is the mainstay of treatment and typically consists of intravenous hydration, fever reduction, and preventive therapy (eg, deep vein thrombosis prophylaxis).^{12,13} The time course of NMS resolution without pharmacologic intervention is difficult to predict and is typically dependent on several factors, such as NMS presentation severity, time to appropriate diagnosis, causative antipsychotic(s), and other contributory or potentiating medications. Additionally, pharmacologic therapy is often utilized to mitigate the clinical symptoms associated with NMS. With the lack of evidence-based recommendations, therapies are selected

TABLE 2: Treatment recommendations based on Woodbury staging^{2,14-16}

Stage	Description/Symptoms	Supportive Care	Medication Interventions
I	Drug-induced Parkinsonism: Mild EPS of rigidity and/or tremor	Reduce or switch antipsychotic	Benzotropine 1 to 4 mg oral/IM/IV 1 or 2 times daily or 1 to 2 mg 2 to 3 times daily OR diphenhydramine 50 mg oral/IM/IV in a single dose; may repeat
II	Drug-induced catatonia: Moderate EPS and some autonomic changes	Discontinue, reduce, or switch antipsychotic	Lorazepam 1 to 2 mg IM or IV every 4 to 6 h
III	Mild, early NMS: Severe rigidity (muscular, cogwheeling), autonomic changes	Discontinue antipsychotics, carefully monitor for progression, and correct risk factors	Lorazepam as above
IV	Moderate NMS: Evolving lead pipe rigidity, severe autonomic changes, elevated CK	Discontinue antipsychotics, manage fluids, initiate cooling measures, correct risk factors, and provide intensive care	Lorazepam as above, OR amantadine 100 mg oral or NGT every 8 h, OR bromocriptine 2.5 to 5 mg oral or NGT every 8 h
V	Severe NMS: Lead pipe rigidity, severe autonomic changes, elevated CK	Discontinue antipsychotics, manage fluids, initiate cooling measures, correct risk factors, and provide intensive care	Dantrolene 1 to 2.5 mg/kg IV every 6 h for 48 h tapered OR amantadine or bromocriptine as above (stage IV)

CK = creatine kinase; EPS = extrapyramidal symptom; IM = intramuscular; IV = intravenous; NGT = nasogastric tube; NMS = neuroleptic malignant syndrome.

based on published case reports and clinical experience. Drug selection and dosing can be determined by use of the Woodberry staging and is summarized in Table 2. Benzotropine and diphenhydramine are anticholinergic agents that combat drug-induced parkinsonian symptoms associated with antipsychotic use. Dantrolene is a skeletal muscle relaxant that directly blocks the release of calcium from the sarcoplasmic reticulum. This mechanism can reduce the pyritic and muscular rigidity features of NMS.¹⁷ Bromocriptine is a dopamine-agonist that helps restore depleted dopamine. The main limitation of therapy with bromocriptine is hypotension, but other potential side effects include acute psychosis, headache, dizziness, fatigue, and nausea. Lorazepam is a benzodiazepine, which modulates the gamma-aminobutyric acid receptor and has an inhibitory effect on muscular rigidity and catatonia.

Historically, NMS-associated mortality was observed in upward of 30% of patients. However, with appropriate and early treatment, mortality is reduced with a typical course lasting approximately 2 weeks.¹² Delayed diagnosis and/or treatment can significantly increase mortality while prolonging the recovery course and increasing the likelihood of persisting catatonic features.¹² Clinical features of increased mortality include disease severity and concurrent medical complications such as myoglobinuria, renal impairment, and structural brain disease.^{1,18,19} Additionally, low-potency antipsychotics and first-generation antipsychotics have poorer outcomes and a higher mortality tendency compared with the high-potency antipsychotic medications and SGAs.^{20,21}

Given their underlying psychiatric disease, resumption of antipsychotic therapy is warranted in the majority of patients. Reexposure to antipsychotic agents is associated with NMS recurrence. Resumption of equipotent antipsychotic doses has been shown to significantly increase the rate of NMS relapse, so a slow and gradual titration is often needed.¹⁷ While no intervention can fully prevent NMS recurrence, measures that can help reduce its likelihood include reintroduction of antipsychotic medications after waiting 2 weeks or more, utilizing low-potency antipsychotics, maintaining hydration, avoiding concurrent lithium, and implementing proper patient education with thorough monitoring for return of symptoms.²²⁻²⁵

Discussion

This patient had an atypical presentation of NMS, and lacked hyperthermia; however, NMS has been previously described without the occurrence of fever.¹⁸ Clinically, the diagnosis of NMS was made based on the presence of altered mental status, autonomic dysfunction (elevated blood pressure and heart rate), elevated CK, and rigid neuromuscular tone in the setting of her recent medication changes. Additionally, utilization of the Delphi method gave a total priority score of 72, which warrants consideration for diagnosis even though the patient would not have met diagnostic criteria according to DSM-5, Levenson, or Nierenberg. It is important to note that none of these criteria specifically address or were designed for diagnosis of NMS with an atypical presentation. As part of the differential diagnosis, related disorders were considered contributory but ruled out. Serotonin syndrome was

initially considered given that the patient was receiving fluoxetine therapy; however, the patient did not exhibit the hallmark gastrointestinal autonomic symptoms of hyperactive bowel sounds and diarrhea or hyperkinetic neuromuscular tone.¹¹ Malignant catatonia was included in the differential diagnosis as the patient's laboratory values were not entirely consistent with NMS, but this process was not thought to be likely given the patient's exposure to antipsychotics and lack of improvement with benzodiazepine therapy. Infectious causes were ruled out due to lacking symptomology as well as temperature and leukocytes within normal limits.

The patient was provided sequential NMS treatment based on the Woodbury staging—first receiving supportive care, discontinuation of antipsychotic therapy, and initiation of diphenhydramine and lorazepam (Table 2). However, the patient was unresponsive to first-line interventions associated with stage I through IV, indicating stage V (severe NMS), which required treatment with dantrolene and bromocriptine. Following initiation of supportive care and combination pharmacotherapy the patient regained autonomic stability and baseline neuromuscular tone.

In this case, the likely etiology of NMS was rapid transition from ziprasidone to risperidone and the elevated dose of antipsychotic therapy. A report of equivalency estimates for SGAs concluded that typical dose equivalents (based on reported minimum oral effective doses) are as follows: risperidone 2 mg/d, olanzapine 5 mg/d, quetiapine 75 mg/d, ziprasidone 60 mg/d, and aripiprazole 7.5 mg/d.²⁶ An advisory committee briefing document reports tolerability when the starting daily dose of oral ziprasidone was initiated at twice the total daily intramuscular (IM) ziprasidone dose from the previous day.²⁷ This is likely to take into account the difference in reported bioavailability of the different dosage forms for the oral and IM dosing of ziprasidone of 30% to 40% and 100%, respectively.²⁷ For the case patient described, the total daily IM dose of 40 mg daily should have resulted in initiation of ziprasidone 80 mg by mouth daily in 2 divided doses. When switching a patient from one antipsychotic to another, a cross-taper approach is typically utilized. This is done to account for differences in receptor binding preferences of each antipsychotic medication, to decrease the likelihood of exacerbating acute psychosis, and to aid in increasing tolerability of the new medication. A direct switch approach should be utilized with caution, and only if the patient is experiencing severe intolerable adverse drug reactions. As always with antipsychotic medications, and especially if using a dose-equivalency approach, the patient must be monitored diligently. Given the aforementioned equivalency estimates, the patient's conversion from ziprasidone 40 mg IM daily (or ziprasidone 80 mg orally) to risperidone 6 mg orally each day would

represent a greater than 2-fold dose increase. The patient was stabilized and tolerating ziprasidone well, so if a medication switch were needed for drug cost and coverage reasons, a cross titration over 7 days (aiming to keep dopamine D2 receptor occupancy as consistent as possible) would have been preferred. Additionally, the patient was receiving concurrent fluoxetine therapy, which, by itself, has been implicated with NMS occurrence.²⁸ Fluoxetine has also been shown to increase plasma risperidone levels via CYP2D6 inhibition by 75%,²⁹ which could have precipitated and exacerbated the clinical presentation of this case of NMS.

Conclusion

This case highlights the ambiguity of NMS diagnosis, especially in the setting of an atypical presentation. Given the high associated mortality and clinical overlap with related syndromes, empiric treatment is warranted when clinically suspected.¹² In cases of atypical presentation, utilization of the Delphi method with a resulting high score may be more beneficial when patients do not exhibit all of the required diagnostic features of the aforementioned (DSM-5, Levenson, Nierenberg) diagnostic criteria. Treatment recommendations and clinical evidence remain limited and vary depending on severity of symptoms. However, deferred diagnosis and treatment contributes to associated mortality. In patients requiring continued use of antipsychotics, resumption of therapy should focus on using the most efficacious agent(s) while trialing an antipsychotic with less potent D2 antagonism as well as limiting the known risks for recurrence. Patient education and continual monitoring are paramount following recovery from NMS.

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