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Neuroleptic Malignant Syndrome: Diagnosis and Management

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ABSTRACT

Objective: To provide an overview of neuroleptic malignant syndrome (NMS) for the general practitioner with the most up-to-date information on etiology, workup, and management.

Data Sources: The search using PubMed included articles with the key words *neuroleptic malignant syndrome*, *antipsychotics*, *neuroleptics*, *diagnosis*, and *treatment of neuroleptic malignant syndrome* published in English from January 2000 to 2017. Single-case reports and articles dealing with the pediatric patient population were excluded.

Study Selection: Over 4,000 articles met the search criteria. After eliminating single-case reports, pediatric cases, reports in pregnant patients, and duplicates, 87 articles underwent screening. Forty-two articles were included in this review.

Results: The literature is rich with cases of NMS associated with the use of neuroleptics and various medications with neuroleptic-like effects. Questions remain with regard to pathophysiology and optimal treatment. NMS is a rare but potentially lethal consequence of the use of antipsychotic medications that requires familiarity with the condition in order to rapidly recognize its onset and appropriately intervene.

Conclusions: NMS mortality rates have declined over the past 30 years, most likely due to early recognition of the syndrome and appropriate intervention. Nonetheless, clinicians, especially primary care clinicians who are using this class of drugs more often for adjunctive treatments, must be cognizant of this syndrome and the implications of their use.

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Neuroleptic malignant syndrome (NMS) was first described in the late 1950s after the introduction of neuroleptic drugs for the treatment of psychotic disorders.[1] In its classic form, NMS is easily recognized, but the lack of specific diagnostic criteria[2,3] coupled with its rare occurrence limits research into its underlying clinical presentation, pathophysiology, and treatment.

Classically, patients have been diagnosed with NMS on the basis of the presence of 4 major symptoms consisting of muscular rigidity, hyperthermia, altered consciousness, and autonomic dysfunction following exposure to neuroleptic medications.[1,4–6] However, there is heterogeneity in the onset, progression, and outcome of NMS. Additionally, there are no universally agreed-upon criteria for the disorder, further confounding research efforts.[2,3]

METHOD

Data Sources and Search Strategy

The search using PubMed included articles with the key words *neuroleptic malignant syndrome*, *antipsychotics*, *neuroleptics*, *diagnosis*, and *treatment of neuroleptic malignant syndrome* published in English from January 2000 to 2017. Single-case reports were excluded with the exception of those including a literature review. Articles dealing with the pediatric patient population were excluded. Articles that included multiple case reviews, data on incidence, pathophysiology of pertinent medications, treatment algorithms, pharmacologic information on causative agents, retrospective studies, or meta-analyses were screened by the authors with emphasis placed on diagnosis, including differential diagnosis and diagnostic criteria, incidence, implicated medications, treatment, and outcome.

Study Selection

Over 4,000 articles met the search criteria. After eliminating single-case reports, pediatric cases, reports in pregnant patients, and duplicates, 87 articles underwent screening. Forty-two articles[1–42] were included in this review. Of these, 26 articles[9–12,14–20,23,26–30,33–35,37–42] contained information on diagnostic criteria, pathogenesis, incidence, suspect medications, workup, treatment, and outcome. An additional 16 references[1–8,13,21,22,24,25,31,32,36] derived from those articles that were initially reviewed that included pertinent studies or data.

RESULTS

International Panel Paradigm of Diagnostic Features

Using the Delphi method, an international multispecialty panel proposed diagnostic criteria for NMS that included the following parameters[3]:

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Clinical Points

- Neuroleptic malignant syndrome (NMS) is a potentially lethal syndrome linked to exposure to dopamine antagonists or abrupt withdrawal of dopamine agonists; virtually all antipsychotics, including typical first-generation antipsychotics and atypical second-generation antipsychotics, exhibit the potential to precipitate NMS.
- NMS is a diagnosis of exclusion, as the differential diagnosis of the symptom complex is broad.
- Treatment of NMS includes withdrawal of the offending dopamine antagonist or reinstatement of the dopamine agonist and supportive care and may include the use of pharmacotherapies and ECT.

1. Exposure to a dopamine antagonist or withdrawal of a dopamine agonist within the 72 hours preceding onset of symptoms
2. Hyperthermia on at least 2 occasions, of greater than 100.4°F or 38°C, measured orally
3. Rigidity
4. Mental status alteration, either reduced or fluctuating level of consciousness
5. Elevation of creatine kinase of at least 4 times the upper limit of normal
6. Sympathetic system lability with at least 2 of the following parameters:
   a. Blood pressure elevation, either systolic or diastolic, ≥25% above baseline
   b. Blood pressure fluctuation ≥20 mm Hg diastolic or 25 mm Hg systolic change occurring within 24 hours
   c. Diaphoresis
   d. Urinary incontinence
7. Hypermetabolism, defined as heart rate increase ≥25% over baseline and respiratory rate increase ≥50% over baseline
8. Absence of other etiologies including infection, toxin exposure, or metabolic or neurologic causes.

Pathophysiology

NMS is generally conceptualized as a disorder triggered in the brain by neuroleptic blockade of the D_2 dopamine receptors located in the hypothalamus and brainstem regulatory systems that in turn culminates in a generalized systemic hypermetabolic syndrome.[7]

In 1999, Gurrera[8] hypothesized that dysregulated sympathetic nervous system hyperactivity explains many of the features of NMS. An exaggerated or extreme sympathetic nervous system dysregulation in response to emotional or psychological stress may constitute a trait vulnerability for NMS. This vulnerability, which may be precipitated by dopamine receptor antagonism, may in turn result in NMS.[8]

Mann and colleagues[9] suggested that there was compelling evidence that disruption of dopaminergic neurotransmission by antipsychotic drug antagonism at the D_2 receptor results in NMS. They proposed that preexisting central dopaminergic hypoactivity (a trait vulnerability) when coupled with adjustments in the dopamine system from acute and repeated exposures to stress could precipitate NMS.

Evidence to date suggests that NMS is associated with virtually all marketed antipsychotics. High-potency first-generation antipsychotics (FGAs) have been assumed to carry a greater risk of precipitating NMS than low-potency drugs and second-generation antipsychotics (SGAs), although this assumption remains unproven.[10–13] In an analysis[11] of 111 cases of either probable or definite NMS reported to the Neuroleptic Malignant Syndrome Information Service, 51% of NMS cases were associated with FGAs and 45% with SGAs. The high-potency FGA haloperidol was identified as the etiologic agent in 44% of all patients.[11]

Pharmacodynamic differences exist between the 2 antipsychotic groups. In general, SGAs express a lower affinity for the D_2 dopamine receptor while being potent antagonists at the 5-HT_{2A} serotonin receptor. The high ratio of 5-HT_{2A} to D_2 receptor occupancy is thought to confer the reduced likelihood of extrapyramidal side effects found with SGAs.[14] Twelve SGAs are currently available in the United States, and 9 of these agents have been implicated in causing NMS (aripiprazole,[12,15] asenapine,[12,15] clozapine,[12,13,15] iloperidone,[15,16] olanzapine,[12,15] paliperidone,[12,15] quetiapine,[12,15] risperidone,[12,13,15] ziprasidone[12,15]).

Three SGAs (aripiprazole, brexpiprazole, cariprazine) are similar in that each has partial agonist activity at the D_2 dopamine receptor and thus may be less likely to exert excessive antagonism than other neuroleptics at this receptor.[14] While clinicians may be tempted to utilize these agents to minimize the risk of inducing NMS, Murri and colleagues[15] reported 14 cases of aripiprazole-associated NMS. Interestingly, they found aripiprazole was associated with a lower frequency of hyperpyrexia, diaphoresis, and tachypnea than other SGA-linked NMS cases. Brexpiprazole and cariprazine did not receive US Food and Drug Administration (FDA) approval until the latter half of 2015, and no data are available to determine their propensity for causing NMS.

Clinical Considerations and Presentation

Virtually all dopamine antagonists have been associated with NMS.[4–6] It is notable that FGAs produced extrapyramidal side effects in 95% or more NMS cases in older studies.[10] High-potency FGAs pose a greater risk for NMS compared to low-potency drugs and newer atypical SGAs.[17–19] A MEDLINE review[10] of 68 cases of NMS demonstrated a positive association between NMS and the use of atypical antipsychotics (clozapine, olanzapine, quetiapine, risperidone). In 62% of cases, the onset of NMS occurred within 2 weeks of instituting the SGA. Of these 68 cases, 3 patients died. Although this finding represents a lower mortality than NMS cases associated with FGAs, SGAs can also be lethal. Furthermore, atypical antipsychotic drug–induced NMS manifestations are similar in nature and severity to those produced by conventional antipsychotic drugs.[10]

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Neuroleptics used in medical settings such as prochlorperazine and promethazine (antiemetics),[4] droperidol (anesthetic and antiemetic),[4] metoclopramide (gastroparesis),[20,21] and amoxapine (antidepressant)[4] have been associated with NMS as well. Psychomotor agitation,[2] parenteral administration routes, rapid dose titration, and higher total daily drug doses have all been associated with increased risk of NMS.[2,4,17] Regardless, NMS usually occurs within the typical therapeutic dosage range of antipsychotics.[4,5,17]

Other systemic risk factors for NMS include exhaustion,[1,4,21,22] dehydration,[1,4,6,21,22] and malnutrition.[23] A prior episode of NMS is a strong risk factor, with 17%–30% of patients developing subsequent NMS after rechallenge with neuroleptics.[4,5]

Patients of both sexes and all ages (youth to elderly) are affected by NMS, but young adult males predominate.[1,4,5,7,21,22,24] Individuals with organic brain syndromes are thought to be at high risk,[1,5,6,8,24] as are those with intellectual disability.[5,10,24]

While estimates of the incidence of NMS have previously ranged from 0.02%–3.23%, pooled data from 16 studies from the late 1980s to 1991 revealed an incidence of about 0.2%.[4] More recent incidence rates reported for NMS are 0.01%–0.02% among individuals treated with antipsychotic medications.[17]

Although there is variability in the course of the disorder, mental status changes are a noted early sign, characterized by delirium or altered consciousness ranging from stupor to coma. Affected individuals may appear alert but dazed and unresponsive, consistent with a presentation of catatonic stupor.[1,4,18,22]

Generalized muscular rigidity, typically described as "lead pipe" rigidity in its most severe form, is considered a cardinal feature of NMS.[1] This symptom may be unresponsive to treatment with antiparkinsonian medications and may be associated with other neurologic signs. These signs include tremor, sialorrhea, akinesia, dystonia, trismus, myoclonus, dysarthria, and dysphagia. The presentation may be accompanied by rhabdomyolysis.[1,22]

In a review focused on the sequential pattern of symptoms in NMS, Velamoor and colleagues[7] found a predominance of 4 signs in most cases. Their analysis revealed that over 70% of the time the following sequence of clinical signs define NMS: mental status changes, then muscular rigidity, followed by hyperthermia and autonomic dysfunction.[7] Thus, in many cases, order sequence may aid the clinician in early detection and intervention in NMS.[7]

In terms of onset, 16% of patients developed signs of NMS within 24 hours of initiating a neuroleptic agent: 66% by 1 week and 96% within 30 days.[4,5] NMS is unlikely to occur after 30 days of instituting a neuroleptic but did so in 4% of patients.[5]

NMS is a diagnosis of exclusion; other disorders must be ruled out, specifically other neuropsychiatric, systemic, and drug-induced hypermetabolic disorders.[4,5] These disorders include other potentially life-threatening conditions such as CNS infections[1,21,22] (acute viral encephalitis, tetanus, and bacterial, fungal, and parasitic infections[1]) and central nervous system mass lesions[4,21] (tumors, abscesses, stroke, or trauma[4]). Endocrinopathies including pheochromocytoma and thyrotoxicosis also share symptom complexes similar to NMS, as do several autoimmune disorders such as systemic lupus erythematosus or mixed connective tissue diseases.[4] Other conditions in the differential when evaluating the patient with fever, autonomic instability, and muscular rigidity include heatstroke,[4,21] serotonin syndrome,[23] toxin exposure and other drug ingestions, malignant hyperthermia following exposure to inhalational anesthetics,[5,6,21–23] parkinsonian hyperthermia syndrome following abrupt discontinuation of dopamine agonists (eg, levodopa,[4,5,21] amantadine[21]), hyperthermia from stimulant (eg, cocaine or amphetamines) or hallucinogen abuse (eg, phencyclidine[4,5]), atropine poisoning from anticholenergics,[4,21,22] and alcohol or sedative withdrawal.[4] In rare instances, patients with schizophrenia or a mood disorder may present with malignant catatonia, which may be indistinguishable from NMS.[20,21]

Catatonia as defined by *DSM-5* is a syndrome of marked psychomotor disturbance requiring at least 3 of 12 symptoms that range from decreased motor activity (eg, stupor, catalepsy) to reduced psychosocial engagement (eg, mutism, negativism) to excessive and peculiar motor activity (eg, agitation, echolalia).[20] It has been recognized since the late 1800s (prior to the advent of antipsychotics) and may be attributed to a mental disorder (eg, psychosis, bipolar or depressive disorder) or a variety of medical conditions (eg, neoplasms, head trauma, encephalitis, diabetic ketoacidosis).[25,26] Catatonia varies in both presentation of symptoms and severity, from mild or simple to malignant.[27,28] Lorazepam administered parentally (eg, 1–2 mg IV) is the initial recommended treatment for catatonia.[26,27,29,30] For patients refractory to lorazepam, electroconvulsive therapy (ECT) is indicated[26,27,29,30] and may prevent a fatal outcome. Considerable controversy remains concerning the difference between malignant catatonia and NMS.[11,20,21,26–28,31] Both conditions share common symptoms (such as fever, rigidity, autonomic instability, and stupor), laboratory abnormalities (elevated creatine phosphokinase, leukocytosis, low serum iron levels), acute worsening of symptoms due to reintroduction of neuroleptics, and response to treatment with both benzodiazepines and ECT.[11,12,26–29,31,32]

No single laboratory abnormality is specific to the diagnosis of NMS.[4,22] Individual patients may display leukocytosis with or without a left shift,[4,22] metabolic acidosis or hypoxia in about 75% of cases,[4,5] and elevations of serum creatine phosphokinase[4–6,22] derived from skeletal muscle in 95% and myoglobinuria in 67%.[4–6] Muscle necrosis from rigidity, hyperthermia, and ischemia may result in acute renal failure.[4,22] Cerebrospinal fluid findings[4–6,21,22] and neuroimaging studies[4,5] are generally normal, but electroencephalograms demonstrated nonfocal generalized slowing in 54% of patients.[4,5] Less consistent findings include hyponatremia,[4] hypernatremia,[4,6] dehydration,[4,6] decreased

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serum iron levels,[4,6] elevated serum catecholamines,[4,8] and coagulopathies.[4]

Treatment and Management

A quandary currently exists for clinicians in how best to proceed with treating NMS. Caroff and colleagues[32] recommend that treatment be individualized given the patient's presentation in regard to duration and severity of NMS. In many cases, NMS is a self-limited iatrogenic disorder, and cessation of antipsychotic medication and medical management may be sufficient to reverse the symptoms.[17]

Supportive care is essential in the treatment of NMS. Immediate withdrawal of the offending neuroleptic agent is the first critical step in the treatment of NMS after which supportive medical therapy is the mainstay of management.[6,17,21,22] Volume replacement should be aggressive, especially since most patients with NMS are dehydrated during the acute phase of the illness.[12,17,22] Serial monitoring and correction of electrolytes are critical.[12,17] Alkalinized fluids or loading with bicarbonate may prevent renal failure.[12,17,33] In cases of extreme hyperthermia, physical cooling measures are paramount.[12,17] Intensive medical monitoring for complications of cardiorespiratory failure, renal failure, aspiration pneumonia, and coagulopathies is indicated.[12,17]

While randomized control trials (RCTs) of pharmacologic treatments are currently lacking, theoretical grounds and numerous clinical reports[11,12,17] provide support for empirical, although non–FDA-approved, approaches.

Benzodiazepines may ameliorate symptoms and hasten recovery, especially in less severe cases.[17,34] A trial of lorazepam (eg, 1–2 mg intravenously every 4–6 hours[34]) is a reasonable first-line clinical intervention in patients with acute NMS, reducing rigidity and fever within 24–48 hours and catatonic symptoms like mutism and immobility.[17,34,35]

Many experts advocate pharmacotherapy with dopaminergic agents. Bromocriptine and amantadine may reverse parkinsonism in NMS, reduce time to recovery, and reduce mortality rates by half when used alone or in combination with other treatments.[17,32] The recommended starting dose of amantadine is 200–400 mg daily given in divided doses and administered orally or via nasogastric tube.[17,34] Bromocriptine is typically started at a dose of 2.5 mg 2 or 3 times a day and increased to a total daily dose of 45 mg if required.[17,34] Bromocriptine may worsen psychosis and can precipitate hypotension and vomiting.[17,21,34] Bromocriptine should be continued for 10 days after resolution of NMS because recurrence may result from premature discontinuation.[34]

Dantrolene is a skeletal muscle relaxant that appears useful in NMS cases associated with extreme hyperthermia and rigidity.[17,32,34] Benzodiazepines or a dopamine agonist may be used concurrently with dantrolene, but dantrolene should not be coadministered with calcium channel blockers since this combination may precipitate cardiovascular collapse.[17,34] Typically, dantrolene is initiated at 1–2.5 mg/kg intravenously, then 1 mg/kg every 6 hours if hyperthermia and rigidity decrease after the first dose.[17,34] Adverse side effects include both respiratory[17,34] and hepatic impairment.[17,21,34] Dantrolene should be continued for 10 days after resolution of NMS symptoms, as patients may suffer a recurrence if it is withdrawn prematurely.[34]

Interestingly, ECT has been determined to be effective in treating NMS.[36] A review[36] of 55 cases of NMS treated with ECT showed that ECT is often an effective approach in many instances. In cases in which prior drug therapy failed, ECT is also effective and is preferred in severe NMS when a prompt response is necessary or if lethal catatonia cannot be ruled out.[36] A total of 6–10 treatment sessions are recommended, with onset of response after a mean of 4.1 treatments. Patients should be monitored for an increase in muscle injury and for hyperkalemia. Response is not predictable based on age, sex, psychiatric disorder, or any particular feature of NMS including catatonia. As in any clinical situation involving capacity to provide informed consent, ethical issues and proxy consent must be addressed.[36]

To date, no RCTs have evaluated the efficacy of the pharmacotherapies stated here or ECT for NMS. Treatment recommendations are based on case series, expert opinion, and consensus.[12,32]

Strawn and colleagues,[17] who have extensive knowledge and expertise with NMS, proposed a treatment algorithm[11] as a tentative guideline in how best to proceed in the treatment of NMS. These investigators note that their algorithm is intended for testing in clinical and research settings, data are based on case series and literature review, and that none of the outlined therapies have FDA approval for treatment of NMS.[11]

Outcome

Once recognized and the offending medication terminated, NMS is usually self-limited unless complications ensue.[4] Mean recovery time is 7–10 days after drug discontinuation,[4,22] and virtually all patients recover within 30 days.[4,5] However, long-acting depot antipsychotics may produce NMS episodes approximately twice as long in duration.[4,22] In some patients, residual catatonic and parkinsonian symptoms of NMS may persist for weeks to months after more fulminate acute symptoms resolve. ECT, even when administered late in the clinical course of NMS, may be highly effective in treating these residual symptoms in patients with symptoms refractory to pharmacotherapy and supportive care.[37]

Fatality rates in NMS of up to 30% have been reported,[4] but more recent literature shows a significant reduction (0%,[35] 10%,[34] 15%[22] fatality rate) in death rates. This reduction is most likely due to greater awareness of the syndrome by clinicians, earlier diagnosis, rapid antipsychotic discontinuation, intervention with supportive care, and use of specific pharmacotherapy.[4–6] Mortality rates have substantially declined since 1984 (11.6% vs 25% before 1984).[24] Myoglobinuria and renal failure are both strong predictors of mortality, with a risk of approximately 50%.[24]

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Death usually results from cardiac or respiratory arrest, aspiration pneumonia, pulmonary emboli, myoglobinuric renal failure, or disseminated intravascular coagulation.[4,12]

Restarting an antipsychotic medication after resolution of NMS is associated with an estimated recurrence rate as high as 30%.[4,5,17] Previous episodes of NMS should be thoroughly investigated for the accuracy of diagnosis.[4] Indications for antipsychotic treatment should be considered carefully by clinicians, and alternative pharmacotherapies weighed.[4,17] Risk factors (eg, dehydration, agitation, concomitant medical illness[4]) should be minimized.[4,17] Also, waiting at least 2 weeks after NMS resolves before restarting any antipsychotic minimizes recurrence.[4,6,17,38] Following a test dose of an antipsychotic, low doses of a low-potency FGA[4,5,17,24] or SGA[17] drug can be titrated gradually with careful monitoring for early signs of emerging NMS.[4,5,17] Informed consent should always be obtained[5,17] before drug rechallenge from both the patient and family members.[17] Generally, NMS has not been found to recur when the same drug is reinstituted at least 4 or more weeks after recovery from the initial episode.[10]

The introduction of partial D_2 dopamine antagonists (aripiprazole, brexpiprazole, cariprazine) may entice clinicians to utilize one of these agents instead of a low-potency FGA or a SGA, as they may consider these medications to be less risky in terms of precipitating another NMS episode. However, Murri and colleagues[15] reported 14 cases of aripiprazole-associated NMS in a recent report. Brexpiprazole and cariprazine have been available for clinical use in the United States for less than 2 years, and we urge clinicians to maintain vigilance should one of these medications be chosen as neuroleptic therapy after NMS until data are available to certify their safety in this at-risk population of patients.

CONCLUSION

NMS is a rare but rapidly progressive, potentially lethal complication associated with the exposure to dopamine antagonists or the withdrawal of a dopamine agonist. Substantial heterogeneity in the onset, progression, and outcome of NMS is well documented.

National trends reflect increased prescribing of psychotropic medications by primary care physicians that outpaces that of psychiatrists.[39] Between August 2006 and July 2007, general practitioners prescribed 37% of all antipsychotics dispensed nationwide.[40] As primary care physicians become increasingly comfortable treating patients with atypical antipsychotics including as adjunctive agents in major depressive disorder,[41,42] they should be cognizant of the consequences of using this class of medication and the need for timely recognition of NMS and management strategies.[41] Increased physician awareness of NMS should lead to earlier recognition, allowing for more rapid treatment and very likely reduced mortality.[10,24]

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