ISSN: 2755-0141

Japan Journal of Clinical & Medical Research

SCIENTIFIC Research and Community

Review Article

Open Access

Neuroleptic Malignant Syndrome and its Clinical Look-Alikes: Diagnostic Insights

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ABSTRACT

Neuroleptic malignant syndrome (NMS) is a rare but life-threatening neurological emergency associated with the idiosyncratic reaction to dopamine-receptor antagonist medications or with rapid withdrawal of dopaminergic medications. While uncommon, this condition can mimic various other acute conditions presenting with acute dysautonomia, fever, and altered mental status, which can lead to delayed recognition and increased morbidity such as residual catatonia, parkinsonism, renal, or cardiopulmonary complications. Therefore, high vigilance, early recognition, and prompt treatment are necessary. In this review article, we aim to elaborate the pathophysiology, clinical features, and comprehensive management of NMS, with a special focus on its various mimicking conditions.

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Received: November 04, 2024; **Accepted:** November 07, 2024; **Published:** November 19, 2024

Introduction

Neuroleptic malignant syndrome (NMS) was first described in the late 1950s after the introduction of neuroleptic drugs for the treatment of psychotic disorders [1]. NMS has been associated with virtually every neuroleptic agent but is more commonly reported with the typical antipsychotics like haloperidol and fluphenazine. Classic clinical characteristics include mental status changes, fever, muscle rigidity, and autonomic instability following the introduction of neuroleptic medications [2-4]. However, due other acute conditions like Serotonin Syndrome, Malignant catatonia, Meningo-encephalitis, malignant hyperthermia etc have similar symptoms making the diagnosis challenging.

Epidemiology

Incidence rates range from 0.01% to 3.2% of patients taking neuroleptic medications [5,6]. The incidence is decreasing due to newer agents, which are less likely to cause NMS. Males are affected twice as often as females, corresponding with exposure patterns to antipsychotic medications [2,7].

Pathophysiology [Figure-1]

The exact aetiology of NMS remains elusive. Most theories centre on dopamine receptor antagonism as a key factor in NMS pathogenesis. It is postulated that central dopamine receptor blockade, particularly in the hypothalamus, may trigger hyperthermia and other autonomic disturbances [8,9]. Additionally, disruption of nigrostriatal dopamine pathways could account for the parkinsonian-like symptoms observed in NMS, such as muscle rigidity and tremor [9,10]. Importantly, other neurotransmitter systems, including GABA, epinephrine, serotonin, and acetylcholine, are likely involved in the pathogenesis, either directly or indirectly [11,12].

An alternative hypothesis suggests that muscle rigidity and damage in NMS may result from direct effects on the peripheral muscular system, possibly through alterations in muscle mitochondrial function [10,13].

Another proposed mechanism involves dysregulation of the sympathetic nervous system [13]. This theory posits that NMS

results from disrupted modulation of sympathetic activity, leading to increased muscle tone and metabolism, as well as uncontrolled sudomotor and vasomotor functions. These disturbances could explain the inefficient heat dissipation and unstable vital signs observed in NMS. In this model, dopamine antagonists are thought to precipitate symptoms by destabilizing normal dopaminergic regulation of efferent sympathetic activity.

Genetic factors may also play a role in NMS susceptibility, as suggested by familial clustering of cases [14].

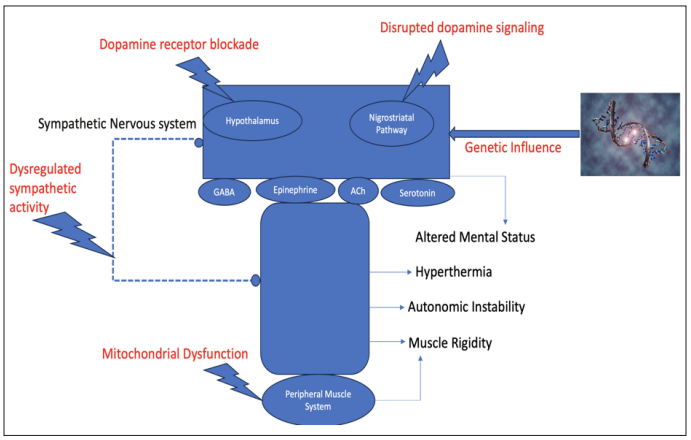

Figure 1: Schematic Diagram of Pathophysiology of Neuroleptic Malignant Syndrome
GABA= Gamma-aminobutyric acid; ACh- Acetylcholine.

Clinical Features

Classically, NMS presents with tetrad of symptoms associated with the use of medications that block dopamine transmission.

- **Altered Mental Status:** Patients typically experience present as an agitated delirium characterized by confusion rather than psychotic symptoms. Catatonic features and an inability to speak may be prominent. As the condition progresses, there's often a deterioration into a profound state of reduced consciousness, potentially culminating in coma [15].
- **Hyperthermia:** Temperature exceeding 38°C (100.4°F) is a common finding. However, the fever may be less frequently observed with newer, atypical antipsychotic medications [16,17].
- **Autonomic Instability:** This can include tachycardia, labile blood pressure, tachypnoea, dysrhythmia and profuse diaphoresis.
- **Muscle Rigidity:** A hallmark feature is generalized muscle rigidity, often described as having a 'lead pipe' quality due to its unyielding nature. In some instances, a superimposed tremor may create a 'cogwheel' sensation upon passive movement of the limbs. Less frequently, patients may experience other movement disorders such as dystonia, opisthotonos, jaw clenching (trismus), chorea, excessive saliva production, difficulty articulating words, and dysphagia.

Diagnostic Evaluation

The diagnostic evaluation for suspected neuroleptic malignant syndrome involves a thorough review of the patient's medical history, a detailed physical examination, and the identification of specific laboratory abnormalities. Key indicators include elevated levels of creatinine kinase (CK). CK levels >1000 IU/L are likely more specific indicators of NMS and the degree of CK elevation is associated with the severity of the disease and can provide insights into the prognosis [5].

Other less specific signs are leukocytosis, slight elevations in lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and liver transaminases. Additionally, various electrolyte imbalances may be present, such as hypocalcemia, hypomagnesemia, hypo- and hypernatremia, and hyperkalemia. Metabolic acidosis and rhabdomyolysis are also important factors to consider.

The DSM-V Criteria for Diagnosing NMS are as Follows [18]:
Major Criteria (all Required)

1. Exposure to Dopamine-Blocking Agent
2. Severe Muscle Rigidity
3. Fever

Other Criteria (at Least two Required)

1. Diaphoresis
2. Dysphagia
3. Tremor
4. Incontinence
5. Altered Level of Consciousness
6. Mutism
7. Tachycardia
8. Elevated or Labile Blood Pressure
9. Leukocytosis
10. Elevated Creatine Phosphokinase

Neuroleptic Malignant Syndrome Mimics

Serotonin Syndrome

It is a medical emergency due to excess serotonin (5-TH) in the brain of patients who use serotonergic medications like selective serotonin reuptake inhibitor (SSRI), serotonin agonists, opioids, some herbal medications and monoamine oxidase inhibitors (MAOIS). It can be challenging to distinguish from neuroleptic malignant syndrome (NMS) due to similar symptoms [19].

The clinical features of serotonin syndrome include excessive sweating, diarrhea, agitation, rapid heartbeat, high blood pressure, overactive reflexes, excessive saliva production, mild muscle stiffness, muscle twitching, dilated pupils, fever, changes in consciousness, delirium, coma, and elevated creatine kinase (CK) levels.

To differentiate between NMS and serotonin syndrome, consider the patient's use of serotonergic medications, the presence of dilated pupils, and hyperreflexia, which are typically present in serotonin syndrome but absent in NMS. Similarly, other features of Serotonin syndrome which are absent in NMS are shivering, myoclonus, and ataxia [20,21].

Malignant Hyperthermia

Malignant hyperthermia (MH) is a life-threatening pharmacogenetic emergency precipitated by potent halogenated inhalational anesthetic agent and succinylcholine, strenuous exercise, working in high temperature and even severe emotional stress.

Pathophysiology of MH includes the triggering agent causing altered ryanodine receptors to remain open, leading to uncontrolled calcium release from the sarcoplasmic reticulum and continuous muscle contraction, resulting in rigidity [22-25]. This ongoing muscle activation increases aerobic and anaerobic metabolism, which elevates oxygen consumption and can cause hypoxia, lactic acidosis, excess CO2 production, and a rise in body temperature.

The symptoms of hyperthermia, muscle rigidity, and autonomic dysfunction in MH are similar to those in Neuroleptic Malignant

Syndrome (NMS), but MH often presents more rapidly and is primarily linked with specific anesthetics.

Withdrawal or Drug Related Syndromes

In several case reports, withdrawal from intrathecal baclofen therapy has been linked to a syndrome resembling Neuroleptic Malignant Syndrome, which included increased muscle tone, autonomic dysfunction, altered mental state, fever, and elevated creatine kinase (CK) levels [26]. The underlying cause is thought to be reduced gamma aminobutyric acid (GABA) activity. Symptoms usually improve when the therapy is resumed, and benzodiazepines can also be beneficial.

Acute intoxication from certain recreational drugs, particularly cocaine and ecstasy (MDMA), can be mistaken for Neuroleptic Malignant Syndrome. Symptoms like hyperthermia and rhabdomyolysis may occur, often linked to increased physical activity and high ambient temperatures. However, rigidity is not typically observed in these situations. Additionally, MDMA use can lead to serotonin syndrome.

Malignant Catatonia

Distinguishing malignant catatonia from Neuroleptic Malignant Syndrome (NMS) can be highly challenging because they share features like hyperthermia and rigidity. Malignant catatonia is often preceded by several weeks of behavioral symptoms, including agitation, psychosis, and catatonic excitement. Motor symptoms can include dystonic posturing, waxy flexibility, and repetitive movements [27,28]. Clinically, differentiating between these two conditions is difficult, as both the history and motor signs can be complex to identify and understand.

Anti-NMDAR Encephalitis

Anti-NMDAR encephalitis is characterized by subacute or acute neuropsychiatric symptoms. Ealy diagnosis and prompt treatment with immunotherapy has a good outcome.

Acute presentation of anti-NMDAR encephalitis can present a diagnostic difficulty as it has common manifestation with NMS like fever, rigidity, hypersalivation, hypertension, diaphoresis, delirium and elevated CK.

Seizure and nonconvulsive status are common in male adults, autonomic instability and movement disorder are common. Anti NMDAR IgG antibodies detected by indirect immunofluorescence in the serum and CSF are diagnostic for the disease.

Management

In managing a Neuroleptic Malignant Syndrome (NMS) crisis, the first step is to stop the use of any antipsychotic or other precipitating drugs. If the syndrome was triggered by the withdrawal of dopaminergic therapy, reintroducing that therapy is advised.

Supportive Management

It's crucial to ensure cardiorespiratory stability, which might require interventions such as mechanical ventilation or antiarrhythmic medications [29]. Maintaining proper hydration is also essential, using intravenous fluids to counteract fluid losses due to fever and sweating. If creatine kinase levels are significantly elevated, administering high-volume IV fluids and urine alkalinization can help prevent kidney damage from rhabdomyolysis [30].

To reduce fever, cooling blankets are typically used, though in severe cases, more aggressive measures like ice packs or ice water gastric lavage may be necessary. While acetaminophen and aspirin might assist in lowering temperature, their efficacy in NMS isn't well established. Managing high blood pressure is important as well; options include clonidine or nitroprusside, the latter of which can help with cooling by causing vasodilation [31,32]. To prevent deep vein thrombosis, heparin or low molecular weight heparin is prescribed. Lastly, benzodiazepines such as lorazepam may be used to alleviate any agitation that arises [33].

Pharmacological Management

Medications like dantrolene, bromocriptine, and amantadine are commonly used despite limited evidence from clinical trials [34]. These drugs are typically reserved for moderate to severe cases to alleviate symptoms such as muscle rigidity and elevated creatine kinase levels. Benzodiazepines (lorazepam or diazepam) are also administered for their sedative and muscle relaxant effects. Dantrolene, dosed at 1-2.5 mg/kg IV, is effective for reducing rigidity and heat production but poses a risk of hepatotoxicity. Bromocriptine, a dopamine agonist, and amantadine offer alternative or adjunct treatments to restore dopaminergic tone. Levodopa has been used in patients with NMS related to antiparkinsonian medications withdrawal. Although anecdotal evidence suggests these medications may hasten recovery and reduce mortality, their benefits are debated, with some analyses showing conflicting results. Despite these uncertainties, these agents are often used due to the severe nature of NMS and lack of other established treatments.

Electroconvulsive Therapy (ECT)

ECT is considered for Neuroleptic Malignant Syndrome when patients do not respond to standard treatments or require non-drug psychotropic intervention. Despite a lack of randomized, controlled studies, ECT is used due to its success in treating malignant catatonia and parkinsonism, and its potential benefit when antipsychotics are unsuitable. Some cases suggest ECT reduces mortality (10.3% vs. 21% with supportive care alone), with clinical improvement often seen after four sessions [35,36]. However, these findings may be skewed by biases and methodological issues.

ECT for NMS involves significant risks, such as cardiovascular complications, seizures, and aspiration pneumonia. Anaesthesia is necessary, but concerns about Malignant Hyperthermia (MH) and ECT-related succinylcholine administration exist. However, no MH cases in NMS patients were noted with succinylcholine use. Nonetheless, hyperkalaemia and arrhythmias related to succinylcholine remain concerns, especially in patients with rhabdomyolysis and autonomic issues.

Prognosis

Most episodes resolve in 7 to 11 days [2,37], with some persisting for six months with lingering catatonia and motor symptoms [38]. Prolonged cases are linked to depot antipsychotic use and structural brain disease [39]. Neurological issues are rare, except after severe hypoxia or prolonged high temperatures. Mortality rates for NMS range from 5 to 20 percent, influenced by disease severity and complications [38, 40-43].

Conclusion

Neuroleptic Malignant Syndrome (NMS) is a critical but rare condition necessitating swift identification and management to minimize complications. Often mimicking other acute disorders, NMS presents diagnostic challenges due to overlapping symptoms.

Understanding its underlying pathophysiology, diverse clinical presentations, and effective management strategies is crucial for clinicians. Emphasis on distinguishing NMS from conditions like serotonin syndrome, malignant hyperthermia and catatonia is essential to avoid misdiagnosis. Comprehensive treatment—from immediate cessation of causative agents to supportive care and possible pharmacological interventions-can significantly improve outcomes.

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