Neuroleptic Malignant Syndrome

Gautam Bhandari

INTRODUCTION
Neuroleptic malignant syndrome (NMS) is an infrequent, but potentially life-threatening neurologic emergency associated with the use of neuroleptic or antipsychotic drugs. It was first described in association with the use of neuroleptic haloperidol in 1960 by Delay et al. Incidence rates for NMS ranges from 0.02% to 3% among patients taking neuroleptic drugs. It is most often associated with typical high-potency neuroleptics (e.g. haloperidol, fluphenazine). However every class of neuroleptic has been implicated, including the low-potency neuroleptics (e.g. chlorpromazine) and newer atypical antipsychotics (e.g. clozapine, risperidone, olanzapine) as well as antiemetic drugs (e.g. metoclopramide, promethazine).

DEFINITION
Neuroleptic malignant syndrome is a rare but life-threatening, idiosyncratic reaction to neuroleptic/antipsychotic medication. It is characterized by fever, muscular rigidity, altered mental status, autonomic dysfunction and elevated creatine phos-phokinase.

PATHOPHYSIOLOGY
Neuroleptic malignant syndrome is thought to be secondary to decreased dopamine (DA) activity in central nervous system (CNS) either from:

- Blockade of dopamine type 2 receptors (D2 receptors)
- Decreased availability of DA itself.

However direct effect on peripheral skeletal muscles may play an additive role (Flow chart 1).

There are three major central dopaminergic pathways: (1) nigrostriatal, (2) mesolimbic/cortical and (3) hypothalamic. Acute blockage of nigrostriatal and hypothalamic DA pathways are believed to result in signs and symptoms of NMS (Figure 1).
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Section 16 PATHOGENESIS OF NEUROLEPTIC MALIGNANT SYNDROME AT CELLULAR LEVEL

Neuroleptic malignant syndrome can occur as a result of changes in pre- or postsynaptic DA signaling (Figure 2 and Table 1). There are two mechanisms:

1. Reduced DA signaling resulting from sudden withdrawal of dopaminergic agents
2. Introduction of agents that block DA signaling (Table 2).

RISK FACTORS

Most consistent risk factors for developing NMS are prominent psychomotor agitation, higher doses of neuroleptics (mean and maximum dose), greater neuroleptic dose increments over a short period of time (increased dose within 5 days and parental administration of drugs [especially depot intramuscular (IM) preparations]. Simultaneous use of two or more neuroleptic drugs and concomitant use of predisposing drugs (e.g. lithium, anticholinergic agents) offer higher risk of NMS.

Other risk factors are increased ambient temperature, dehydration, history of organic brain syndrome or affective disorder, genetics, young age and male gender, past history of NMS, trauma, infection, malnutrition, alcoholism, premenstrual phase in females and thyrotoxicosis.

HISTORY AND CLINICAL FEATURES

Neuroleptic malignant syndrome is more likely to develop following initiation of neuroleptic therapy or an increase in the dose of drug. The onset can be within hours, but on an average, it is 4–14 days after initiation of therapy.

<table>
<thead>
<tr>
<th>Presynaptic</th>
<th>Synaptic</th>
<th>Postsynaptic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine (DA) depletors</td>
<td>Cessation of the DA precursor, levodopa (L-DOPA)</td>
<td>Cessation of postsynaptic DA agonists such as pergolide, bromocriptine</td>
</tr>
<tr>
<td>Reduced DA precursor</td>
<td>Cessation of COMT inhibitors (e.g. tolcapone or entacapone)</td>
<td>Amphetamines, cocaine</td>
</tr>
</tbody>
</table>

TABLE 1 Pathogenesis of neuroleptic malignant syndrome (NMS) (secondary to drugs), at cellular level

<table>
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<tr>
<th>Presynaptic</th>
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<td>Tetrabenazine reserpine</td>
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Abbreviations: COMT, Catechol-O-methyltransferase; D2 Receptor, dopamine type 2 receptor; MAO, Monoamine oxidase; HVA, Homovanillic acid; 3-MT, 3-methoxytyramine; 3-IP, 3-iodopropyl-tyramine; L-DOPA, levodopa; DA, Dopamine; 3-MT, 3-methoxytyramine; HVA, Homovanillic acid; MAO, Monoamine oxidase.
The four defining features that characterize NMS are:
1. Motor symptoms
2. Altered mental status
3. Hyperthermia
4. Autonomic instability.

Motor Symptoms
Because of basal ganglia dopaminergic involvement, the primary motor feature is rigidity or the so-called “lead-pipe rigidity”. Other motor abnormalities include akinesia/bradykinesia, dystonia, mutism, chorea, dysarthria and tremors.2

Altered Mental Status
Changes in the mental status ranging from confusion, delirium and stupor to coma are common in NMS.11

Hyperthermia
Fever more than 38°C is commonly seen and sometimes it exceeds 41°C.12

Autonomic Instability
Autonomic dysfunction manifests with respiratory irregularities, cardiac arrhythmias, varying blood pressure (BP), incontinence and diaphoresis.2,13

DIAGNOSTIC CRITERIA
Diagnostic criteria include:
• The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria (Table 3)
• Levenson’s clinical criteria (Table 4).
All the three major or two major and four minor, criteria suggest a high probability of NMS, if supported by clinical history.

INVESTIGATIONS
Laboratory Studies
Laboratory studies include:
• Elevated serum creatine kinase (CK)
• Other laboratory abnormalities.

Elevated serum creatine kinase: In NMS, CK is typically more than 1,000 IU/L and can be as high as 100,000 IU/L.2,3,14 Elevated CK levels reflect rhabdomyolysis secondary to muscular rigidity. The degree of CK elevation seems to correlate directly with disease severity and higher levels are consistent with a worse prognosis.2

Other laboratory abnormalities: Other most consistent finding is leukocytosis with a white blood cells (WBC) count 10,000–40,000.2,13 A left shift may be present.

Mild elevation of lactate dehydrogenase (LDH), alkaline phosphatase and liver transaminases are common. Electrolyte abnormalities like hypocalcemia, hypomagnesemia, hypo- or hypernatremia, hyperkalemia and metabolic acidosis are frequently observed. Myoglobinuric acute renal failure can result from rhabdomyolysis. A low serum iron concentration (mean 5.71 µmol/L, normal 11–32 µmol/L) is commonly seen in NMS, and is sensitive but not specific marker for NMS among acutely ill.

Other Investigations
In severe NMS cases, coma and stupor may be present. In these circumstances, imaging studies and spinal tap cerebrospinal fluid (CSF) may be performed to evaluate for an alternative cause or determine if there is an accompanying cerebral edema from ongoing metabolic derangements. A brain computed tomography (CT) scan/magnetic resonance imaging (MRI) and CSF may be normal.
INTRODUCTION

Neuroleptic malignant syndrome is a medical emergency, and can lead to death if untreated. The first step is prompt recognition of NMS and immediate withdrawal of the neuroleptic agents, and also excluding other medical conditions. Supportive medical care, specific pharmacotherapy and electroconvulsive therapy (ECT) are useful in complete treatment.

Supportive Care
Aggressive therapy is needed in NMS. However, supportive care in NMS is absolutely essential. Complications are common and severe, even fatal. These include:
- Dehydration
- Electrolyte imbalances
- Acute renal failure associated with rhabdomyolysis
- Cardiac arrhythmias including torsade de pointes and cardiac arrest
- Myocardial infarction
- Cardiomyopathy
- Respiratory failure from chest wall rigidity, aspiration pneumonia, pulmonary embolism
- Deep vein thrombosis (DVT)
- Thrombocytopenia
- Disseminated intravascular coagulation (DIC)
- Seizures from hyperthermia and metabolic derangements
- Hepatic failure
- Sepsis.

TREATMENT

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Specific Pharmacotherapy

Commonly used agents are dantrolene, bromocriptine and amantadine. Other drugs used are levodopa (L-DOPA) and carbidopa, apomorphine subcutaneously (SC), IV clonidine and benzodiazepines (Table 5).

Clinical preferences seem to determine the use of bromocriptine and/or dantrolene. Since bromocriptine is not available in injection form, it can be given only orally or through a nasogastric tube. It is usually well tolerated in psychotic patients. It can be combined with supportive care in mild to moderate NMS patients.

In patients who have severe rigidity, rhabdomyolysis and extreme hyperthermia, IV dantrolene may be preferred with or without bromocriptine. Alternatively, initial management may include IV dantrolene followed by oral bromocriptine. Treatment is continued for at least 10 days after resolution of the episode, as neuroleptics are cleared slowly from the body systems. Early withdrawal of the treatment can precipitate recurrence of NMS. With depot neuroleptics, treatment should be continued up to 2-3 weeks beyond clinical recovery. After resolution and stabilization of symptoms, treatment of NMS should be tapered off gradually with serial follow-up of CK and myoglobin levels. Sudden withdrawal of treatment inspite of recovery is discouraged.

Electroconvulsive Therapy

Electroconvulsive therapy improves some of the components of the syndrome like fever, sweating and the level of consciousness. It is speculated that it works by facilitating brain DA activity. Indications of ECT are severe NMS, refractory to medical therapy (> 48 hours) and when it is not possible to differentiate a diagnosis of NMS from ALC.

PREGNANCY AND NEUROLEPTIC MALIGNANT SYNDROME

Hyperthermia associated with NMS during first trimester of pregnancy may cause birth defects such as anencephaly. Bromocriptine is relatively safe for treating NMS during pregnancy.

PROGNOSIS

Most episodes of NMS resolve within 2 weeks and reported mean recovery times are 7-11 days. Cases persisting for 6 months with residual catatonia and motor signs are reported. Risk factors for a prolonged course are depot antipsychotic use and concomitant

Malignant Syndrome

1. Conditions related to NMS
2. Conditions unrelated to NMS.

Conditions Related to Neuroleptic Malignant Syndrome
- Serotonin syndrome
- Malignant hyperthermia
- Malignant catatonia
- Acute lethal catatonia (ALC)
- Central cholinergic syndrome
- Metabolic encephalopathy/encephalitis.

Conditions Unrelated to Neuroleptic Malignant Syndrome
- Central nervous system infection (meningitis/encephalitis)
- Heat stroke
- Delirium tremens
- Parkinsonism
- Seizures
- Acute porphyria
- Septic shock
- Tetanus
- Strychnine toxicity
- Pheochromocytoma.

Differential Diagnosis of Neuroleptic Malignant Syndrome

Differential diagnosis of neuroleptic malignant syndrome can be broadly, divided into two categories:
1. Conditions related to NMS
2. Conditions unrelated to NMS.

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Intensive monitoring and supportive treatment need admission to the intensive care unit (ICU). The following supportive treatment should be provided:
- Discontinue neuroleptic agent or precipitating drug
- Maintain cardiorespiratory stability. Mechanical ventilation, antiarrhythmic agents or pacemakers may be required.
- Maintain euvolemic state using intravenous (IV) fluids. Insensible fluid loss from fever and diaphoresis should also be considered. If CK is very elevated, high volume IV fluids and urine alkalization with IV sodium bicarbonate [NaHCO3] may help to prevent renal failure from rhabdomyolysis.
- Lower the temperature using cooling blankets, ice cold water, gastric lavage and ice packets in axilla and cold sponging. Antipyretics may be used.
- Lower BP, if markedly elevated. Clonidine is effective in this setting.
- Prescribe heparin or low-molecular-weight heparin (LMWH) for DVT prevention
- Use benzodiazepines (e.g. clonazepam or lorazepam 0.5–1 mg) to control agitation if necessary.

Table 5

<table>
<thead>
<tr>
<th>Indications</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroleptics</td>
<td>Dantrolene, Bromocriptine, Amantadine</td>
</tr>
<tr>
<td>ALC</td>
<td>Bromocriptine, Dantrolene</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Benzodiazepines (L-DOPA)</td>
</tr>
<tr>
<td>L-DOPA</td>
<td>Apomorphine, Carbidopa</td>
</tr>
<tr>
<td>ECT</td>
<td>Electroconvulsive Therapy</td>
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PROGNOSIS

Most episodes of NMS resolve within 2 weeks and reported mean recovery times are 7–11 days. Cases persisting for 6 months with residual catatonia and motor signs are reported. Risk factors for a prolonged course are depot antipsychotic use and concomitant...
TABLE 5 | Specific pharmacotherapy: Commonly used agents and drugs

<table>
<thead>
<tr>
<th>Category</th>
<th>Bromocriptine</th>
<th>Dantrolene</th>
<th>Amantadine</th>
<th>Levodopa and carbidopa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Central dopamine (DA) agonist</td>
<td>Skeletal muscle relaxation via inhibition of calcium release from sarcoplasmic reticulum</td>
<td>Release DA from dopaminergic terminals and other central sites</td>
<td>Dopamine agonist</td>
</tr>
<tr>
<td>Dose</td>
<td>Oral: 2.5–10 mg/d four times a day with increments of 2.5 mg tid every 24 hours until a response is seen or up to 60 mg/d</td>
<td>Oral: 50–200 mg/d</td>
<td>100–300 mg bd</td>
<td>25–250 mg tds or qid</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Dose-limiting hypotension, psychosis, nausea and so forth</td>
<td>Hepatotoxicity (especially with doses &gt; 10 mg/kg/d)</td>
<td>Hepatotoxicity, uncontrolled psychosis, seizures</td>
<td>MI, arrhythmia, asthma, peptic ulcer, dyskinesia</td>
</tr>
</tbody>
</table>

Abbreviations: tid, Ter in die (Three times a day); bd, Bis in die (Twice a day); tds, Ter die sumendus (Three times a day); qid, Quater in die (Four times each day); MI, Myocardial infarction

structural brain disease. Most patients recover without neurologic sequelae, except where there is severe hypoxia or grossly elevated temperatures for a long duration. Reported mortality rates for NMS are 5–20%. Disease severity and the occurrence of medical complications are the strongest predictors of mortality.

### Restoring Neuroleptics

Patient restarted on neuroleptic agents may or may not have recurrent NMS episode. Early resumption of neuroleptic therapy, use of high-potency drugs, parental neuroleptics and concomitant use of lithium, appear to be high-risk factors for recurrence of NMS.

If neuroleptic medication is required, the following guidelines may minimize the risk of NMS recurrence: 1,2,3 However, none of these guarantee either success or failure:

- Wait for at least 2 weeks before restarting therapy
- Use low-potency rather than high-potency drugs
- Start with low doses and titrate upward slowly
- Avoid concomitant lithium
- Avoid dehydration
- Carefully monitor for symptoms of NMS.

### CONCLUSION

Neuroleptic malignant syndrome is a rare, but life-threatening medical emergency following usage of neuroleptics. Early recognition and prompt treatment has shown encouraging outcome (reduced mortality).

### ACKNOWLEDGMENT

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### REFERENCES