Neuroleptic Malignant Syndrome (NMS)

Background
Neuroleptic Malignant Syndrome (NMS) is a rare, acute and life threatening disorder of thermoregulation and neuromotor control. It is characterised by muscle rigidity, hyperthermia, altered consciousness and autonomic dysfunction through dopamine blockage following exposure to antipsychotic medication. It can range from mild with few signs and symptoms to an acute, severe syndrome that should be considered a medical emergency. NMS generally develops within the first 2 weeks of an antipsychotic drug being initiated or after a change of dose.

Incidence
Incidence of NMS is difficult to estimate as antipsychotic use has changed over time and awareness of the condition has increased. Incidence rates have decreased from 3% since it was first described in 1960 to around 0.01%-0.02% in patients treated with antipsychotics.

Aetiology
The exact cause of NMS is unknown, but it is likely primarily related to central inhibition of dopaminergic transmission giving rise to autonomic instability and dysregulation. All antipsychotics, both first generation (FGAs) and second generation (SGAs) can cause NMS at any dose, although it is more likely with high dose, rapid dose escalation and first generation antipsychotics (FGAs). Neurotransmitter depletion occurs with FGA & SGA treatment and abrupt withdrawal of any dopamine agonists such as anti-Parkinson’s agents.

The concurrent use of other medications which can affect dopamine concentrations (e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, domperidone, metoclopramide and lithium) have also be implicated. Combinations of antipsychotics with SSRIs or cholinesterase inhibitors may increase the risk of NMS; NMS–type syndromes induced by SGA/SSRI combinations may share their symptoms and pathogenesis with serotonin syndrome. Conditions where central dopamine handling is affected can also predispose individuals to the syndrome, such as Parkinson’s Disease or Wilson’s disease.

Summary of risk factors

<table>
<thead>
<tr>
<th>Strong</th>
<th>Weak</th>
<th>Other</th>
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<tbody>
<tr>
<td>High potency FGAs</td>
<td>Older age</td>
<td>Abrupt withdrawal of anticholinergic agents</td>
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<td>Recent or rapid dose increase</td>
<td>Pre-existing agitation</td>
<td>Organic brain disease</td>
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<td>Antipsychotic polypharmacy</td>
<td>Male gender</td>
<td>Alcoholism</td>
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<td>Intramuscular administration</td>
<td>Pre-existing dehydration</td>
<td>Parkinson’s disease or Wilson’s disease</td>
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<td>Abrupt withdrawal of dopaminergic drugs</td>
<td>Exposure to other dopamine antagonists e.g. metoclopramide, lithium, certain antidepressants</td>
<td>Hyperthyroidism</td>
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<td>Structural brain abnormality</td>
<td>Catatonia</td>
<td>Younger age</td>
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Diagnosis of NMS

The “classic” picture of NMS consists of a tetrad of symptoms: altered mental state, fever, extrapyramidal symptoms, and autonomic instability, although there can be a significant heterogeneity in the presentation. SGA-induced NMS may present without some (if not all) of these symptoms and there have been ‘atypical’ NMS cases where hyperthermia and muscle rigidity has developed either much slower or been completely absent. It is therefore paramount that all possible symptoms are considered (see table 1) when making a diagnosis.

### Table 1: Groups of symptoms and signs of Neuroleptic Malignant Syndrome.

<table>
<thead>
<tr>
<th>Altered Mental State</th>
<th>Hyperthermia</th>
<th>Autonomic Instability</th>
<th>Muscle Rigidity</th>
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<tbody>
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<td>Confusion</td>
<td>Temperatures &gt;38.5°C</td>
<td>Fluctuating Blood Pressure</td>
<td>Creatinine Kinase markedly raised (&gt;200 – 100,000 IU/L)</td>
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<td>Delirium</td>
<td>Tachycardia</td>
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<td>Extrapyramidal symptoms (Muscle stiffness)</td>
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<td>Stupor</td>
<td>Excessive Sweating (Diaphoresis)</td>
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<td>Trismus (Jaw contraction)</td>
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<td>Coma</td>
<td>Tachypnoea</td>
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<td>‘Lead pipe’ rigidity</td>
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<td>Grand mal seizures</td>
<td>Excessive Saliva Production (Sialorrhea)</td>
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<td>Rhabdomyolysis</td>
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<td>Drowsiness</td>
<td>High arterial pressure</td>
<td></td>
<td>Opisthotonus (spinal contraction)</td>
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<td></td>
<td>Incontinence</td>
<td>Babinski’s sign (abnormal flexion of the toes)</td>
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<td>Chorea</td>
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Differential diagnoses

Although a positive diagnosis is primarily symptom-based, NMS can mirror other conditions with little variation in presentation, and so these must be excluded before a definitive diagnosis is made (Table 2).

Laboratory findings

- Raised creatinine kinase (CK) at least four times upper limit of normal (can be asymptomatic)
- Abnormal LFTs
- Leucocytosis
- ECG abnormalities
- Electrolyte disturbances may also be present.

Temperatures above 40°C or renal failure secondary to rhabdomyolysis are indicators of severe NMS and are associated with a poorer prognosis and urgent medical attention is required. Further complications can include seizures, disseminated intravascular coagulation, respiratory failure, and aspiration pneumonia.
Differential diagnosis | Distinguishing features
---|---
Serotonin syndrome | Rapid onset after administration of a serotonergic drug, hyperreflexia, clonus, diarrhoea. (See SS guideline) *hyperlink*
Malignant hyperthermia | Usually after exposure to anaesthetics or depolarising muscle relaxants in genetically susceptible people; rapid onset, trismus (lockjaw)
Catatonia | Withdrawal, predominance of motor abnormalities, absence of hyperthermia, gradual evolution of presentation
Infection/sepsis | CNS or systemic signs and symptoms of infection
Heat stroke | Rapid onset, occurs during prolonged elevations in ambient temperatures; diaphoresis; muscle rigidity usually not present
Toxicity/overdose of other drugs e.g MAOIs, lithium | 
Drug abuse/adverse reactions e.g. cocaine, amphetamines, CNS stimulants | History of drug abuse, overdose symptoms
Alcohol or sedative withdrawal | History of alcohol or sedative abuse
Metabolic conditions e.g. dehydration, hyponatraemia, hypokalaemia | Signs and symptoms of dehydration, abnormal U&Es

*Table 2: Differential diagnosis*

**Treatment**

The first step of treatment is to immediately withdraw all potential causative medicines. Subsequent management depends on the patient’s presentation:

- Correct dehydration and hyperthermia
- Monitor temperature, pulse and blood pressure
- Sedate with benzodiazepines as necessary
- Measure WCC, U&Es, LFTs and CK
- In case of a medical emergency, transfer patient to acute medical care
- Treat acute symptoms: dantrolene, a muscle relaxant and/or bromocriptine, a dopaminergic agent and/or artificial ventilation may be required

**Reintroduction of Antipsychotics**

- Risk of recurrence of NMS can be as high as 30%\(^1\)
- Allow symptoms to completely resolve before re-introducing antipsychotic, leave a gap of at least 2 weeks and avoid causative agent
- Establish if any there is any previous history of similar reaction
• Document NMS and causative agent within clinical notes as an adverse drug reaction
• Document clearly indications for antipsychotics
• Reduce any modifiable risk factors
• Choose an antipsychotic structurally unrelated to the causative agent or a drug with low dopamine affinity (quetiapine or clozapine)
• Avoid depot/LAI antipsychotic preparations and high potency FGAs
• Begin with a low dose and titrated slowly with close monitoring of physical and biochemical parameters e.g. temperature, BP, pulse, muscle tone, and CK

**KEY SUMMARY**

- **NMS is a rare but potentially fatal adverse reaction, most commonly seen with antipsychotic agents**
- **SGAs may have a lower incidence of NMS than FGAs**
- **Combinations of antipsychotics or antipsychotics with lithium or antidepressants may increase the risk of NMS**
- **Rarely associated with withdrawal or reduction of dose of dopamine agonists and use of metoclopramide and domepridone**
- **Symptoms include hyperthermia, autonomic instability, altered consciousness and muscle rigidity**
- **Laboratory findings include elevated CK, leucocytosis and impaired LFTs**
- **NMS is a diagnosis of exclusion, so differential diagnoses must be ruled out**

If NMS is suspected, discuss with senior colleagues and if clinically unwell, refer to acute hospital.

Reintroduction of all antipsychotics should only be initiated by senior medical staff.

**References**