Neuroleptic Malignant Syndrome

Synonyms: NMS, malignant neuroleptic syndrome

This is a rare but potentially life-threatening idiosyncratic reaction to neuroleptic drugs. It causes fever, muscular rigidity, altered mental status and autonomic dysfunction. The syndrome is usually associated with potent neuroleptics such as haloperidol and fluphenazine.

The underlying pathological abnormality is thought to be central D2 receptor blockade or dopamine depletion in the hypothalamus and nigrostriatal/spinal pathways. This leads to an elevated temperature set-point, impairment of normal thermal homeostasis and extrapyramidally induced muscle rigidity. However, this does not explain why it sometimes occurs with low-potency neuroleptic drugs or other medication without known antidopaminergic activity. It is thought that other mechanisms such as changes in skeletal muscle calcium metabolism or sympathoadrenal hyperactivity may be involved. The condition shares many features with the serotonin syndrome and malignant hyperpyrexia. It presents a diagnostic challenge.

Epidemiology\[1\]

- Pooled data from 1966 to 1997 suggested the incidence of neuroleptic malignant syndrome (NMS) ranges from 0.2% to 3.2% of psychiatric inpatients receiving neuroleptics.
- As newer neuroleptic agents have become available, the incidence has dropped to around 0.01% to 0.02%.
- Incidence is higher in those aged under 40 years and in males, probably reflecting use of antipsychotics. However, it can occur at any age in patients receiving precipitating medication.\[5\]
- A review of the literature between 1990-2008 found 20 cases in patients between the ages of 11-18.\[3\]

Risk factors for developing NMS\[1\]
- Use of neuroleptic drugs and genetic/metabolic susceptibility.
- Withdrawal of anti-Parkinsonian medication.
- Use of high doses and of depot preparations.
- Patient agitation or catatonia.
- High ambient temperature and dehydration appear to increase risk of the syndrome.
- A previous episode of NMS significantly increases the risk of a future similar reaction.\[4\]
- Less commonly, use of other agents with central D2 receptor antagonist activity may cause the syndrome:
  - Prochlorperazine.
  - Promethazine.
  - Atypical antipsychotics such as clozapine, risperidone.
  - Anticholinergic drugs.
  - Metoclopramide.
  - Amoxapine (tricyclic now discontinued).
  - Lithium.

Presentation

Symptoms
- Patients may report dyspnoea (due to hypoventilation caused by muscle rigidity), dysphagia or difficulty walking with the development of a shuffling gait.
- There may be increasing tremor or involuntary movements.
- Rarely, there may be oculogyric crises, opisthotonos, seizures or chorea.

NMS is most common after initiation or increase in dosage of neuroleptic therapy and in 90% of cases this occurs within 10 days.\[6\] The onset is usually gradual over 1 to 3 days and tends to occur within four weeks of starting or increasing neuroleptic medication. However, it can occur at any time in those taking neuroleptics. There is always a history of taking neuroleptics or other relevant agents within the preceding four weeks.

Symptoms can persist for up to 5 to 10 days after discontinuation of the offending drug, or longer if depot medication.

Signs
- There will be hyperthermia with temperature above 38°C.
- Muscular rigidity (lead-pipe type) will always be present.
- There is likely to be an alteration in mental status with confusion or agitation and altered consciousness.
- Autonomic instability may manifest as pallor, tachycardia, fluctuating blood pressure, excessive sweating/salivation, tremor and incontinence.
Diagnostic features of NMS\[6\]
- Neuroleptics within 1 to 4 weeks.
- Hyperthermia (above 38°).
- Muscle rigidity.
- Five of the following:
  - Changed mental status.
  - Tachycardia.
  - Hypotension or hypertension.
  - Tremor.
  - Incontinence.
  - Diaphoresis (excessive sweating) or sialorrhoea.
  - Increased creatine phosphokinase (CPK) or urinary myoglobin.
  - Metabolic acidosis.
  - Leukocytosis.
  - Exclusion of other illnesses (neuropsychiatric, drug-induced, systemic).

Differential diagnosis
- Simple dystonic/akathisia reaction to neuroleptics (usually responds rapidly to anticholinergics).
- Serotonin syndrome.
- Malignant hyperpyrexia.
- Recreational drug toxicity, especially cocaine, amphetamines, 3,4-methylenedioxy-N-methylamphetamine (MDMA) - also known as ‘ecstasy’.
- Phenothiazine-related heatstroke (no rigidity and absence of sweating, the cause of pyrexia in this condition).
- Lethal catatonia (rare psychiatric syndrome - catatonia with rigidity ± raised creatine kinase (CK), usually no autonomic involvement or involuntary movement).
- Organophosphate poisoning.
- Heatstroke.
- Encephalitis (including herpes simplex encephalitis and rabies).
- Hyperthermic reaction to monoamine-oxidase inhibitors.
- Polymyositis.
- Rhabdomyolysis.
- Other forms of poisoning (for example, strychnine).
- Other drug toxicity (anticholinergics, selective serotonin reuptake inhibitors).

Investigations\[1, 5\]
- FBC often shows leukocytosis.
- U&Es may show metabolic disturbance due to acidosis or acute kidney injury.
- Hypocalcaemia is a frequent association.
- Arterial blood sample to assess acid-base balance.
- LFTs may show elevated transaminases and lactate dehydrogenase (LDH) of muscle origin.
- CK is usually elevated.
- Urine myoglobin should be checked.
- Coagulation studies (particularly prothrombin time, activated partial thromboplastin time and international normalised ratio (INR)) should be checked (to detect coagulopathy).
- A urinary drug screen should be performed (particularly for salicylates, cocaine and amphetamines).
- If sepsis is suspected then blood and other relevant cultures should be taken.
- Imaging may be indicated:
  - CXR should be considered if sepsis is suspected.
  - CT scan of the head, in order to exclude other diagnoses.
- Lumbar puncture may be required to exclude other diagnoses (particularly where there is fever and altered mental status). There are no significant cerebrospinal fluid (CSF) findings in NMS other than raised protein.

Management\[7\]
- Airway and breathing need to be protected if there is evidence of compromise. Severe cases may require circulatory and ventilatory support.
- Agitated patients require intravenous (IV) benzodiazepines. Physical restraint is best avoided or minimised, as it can worsen the hyperthermia.
- The offending drug should be discontinued.
- IV fluids should be given for dehydration.
- If there has been a recent overdose of the agent then activated charcoal may help to prevent absorption.
- Cooling devices and antipyretics are used to treat hyperthermia.
- If rhabdomyolysis and acute kidney injury occur then alkalinisation of urine and dialysis are often required.
- Dopaminergic drugs, such as bromocriptine and amantadine and muscle relaxants, such as dantrolene sodium, are frequently used in severe cases but there is little empirical evidence for their efficacy. However, there are many anecdotal reports of their usefulness.
• Electroconvulsive therapy (ECT) is sometimes used if medication fails to improve the condition and there appears to be some evidence to support its use.

Prognosis\textsuperscript{[1, 8]}

Mortality has reduced from 20-30% and is now reported as 5-11.6%. Death is usually caused by cardiovascular collapse, respiratory failure, myoglobinuric acute kidney injury, arrhythmias or diffuse intravascular coagulation. Morbidity results from respiratory failure, acute kidney injury, seizures and arrhythmia.

If acute kidney injury develops during an episode of NMS this increases mortality up to 50%.

Once oral neuroleptics are stopped, the condition can last for 2-14 days; for depot neuroleptics, the period may be up to 21 days.

The outlook is good on the whole if there:

• Is early recognition of the condition.
• Is adequate supportive care and treatment.
• Are no complications.

Complications\textsuperscript{[1, 9]}

• Cardiac arrest.
• Rhabdomyolysis.
• Acute kidney injury.
• Seizures.
• Respiratory failure.
• Disseminated intravascular coagulation.
• Aspiration pneumonitis.
• Deterioration in psychiatric condition due to drug withdrawal.
• Infection.
• Hepatic failure.
• Pulmonary embolism.
Prevention

- Awareness of the condition and consideration of the diagnosis in those with relevant symptoms, on neuroleptics, is central to early diagnosis.
- Monitoring for features of the syndrome after changes in neuroleptic medication can assist early diagnosis.
- Early diagnosis and withdrawal of any offending drug will arrest development of worsening symptoms.
- It is important to give a warning of the risk of recurrence. Patients should be actively encouraged to inform healthcare providers of their susceptibility and given good written information to assist in this process. There is a very good case for use of medical emergency identification jewellery or similar.

Further reading & references

6. Neuroleptic Malignant Syndrome; National Organization for Rare Diseases, 2004

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