NEUROLEPTIC MALIGNANT SYNDROME

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OVERVIEW

Definition:

Neuroleptic malignant syndrome (NMS) is a life-threatening adverse drug event associated with dopamine-blocking agents

Etiology:

High potency first generation antipsychotics (most common) e.g. haloperidol, chlorpromazine

Second generation antipsychotics e.g. olanzapine, clozapine

Other dopamine antagonists e.g. metoclopramide, promethazine

Risk factors:

Genetic predisposition

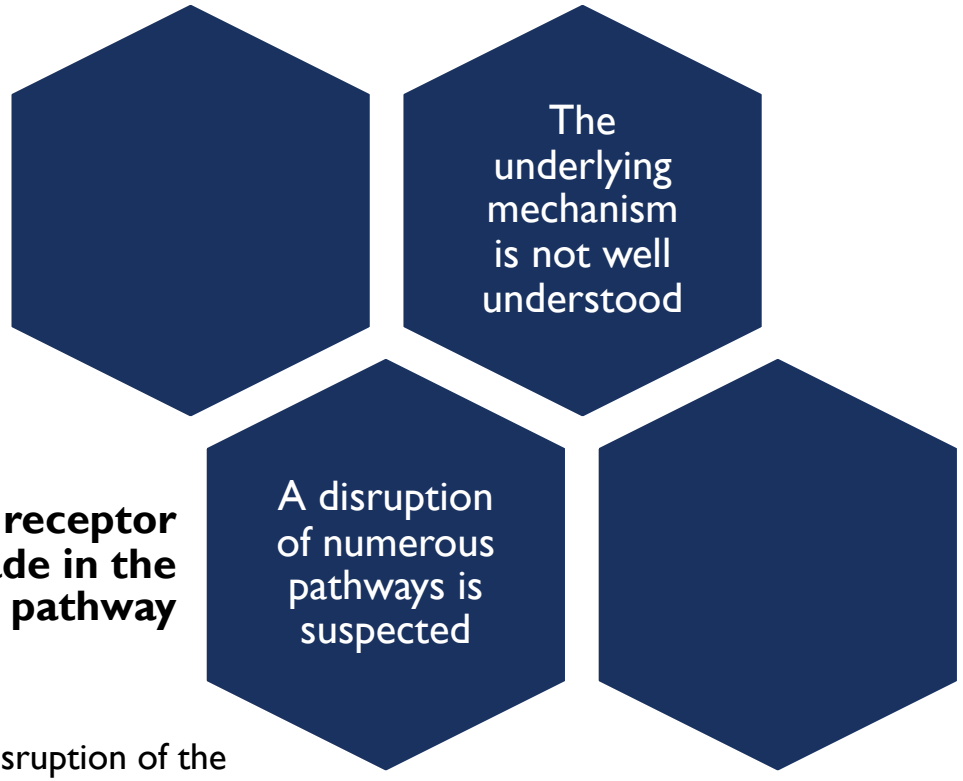
Concurrent use of multiple neuroleptic agents or lithium

Catatonia

EPIDEMIOLOGY

- Incidence due to the use of anti-dopaminergic agents:
  - Reported incidence ranges from 0.01% to 3.2%[1]
  - Decreasing with newer (atypical) antipsychotic agents
  - M:F ratio is 2:1
  - Most cases occur in young adults

PATHOPHYSIOLOGY



Central D_2 receptor blockade in the nigrostriatal pathway

Exacerbated by a preexisting central hypodopaminergic activity[2]

Disruption of the sympathoadrenalmedullary pathways[3]

CLINICAL FEATURES

- Exposure to anti-dopaminergic agent(s)
- Hyperthermia
- Parkinsonism
  - Muscle rigidity (lead-pipe rigidity)
  - Akinesia
  - Tremor
- Mental status change (encephalopathy)
  - Altered level of consciousness
  - Delirium
  - Stupor
  - Mutism
- Autonomic instability
  - Tachycardia, dysrhythmias
  - Labile blood pressure
  - Diaphoresis
  - Incontinence

INVESTIGATION

- Laboratory studies:
  - Blood tests –
    - ↑ ↑ Creatine kinase
    - ↑ ↑ Leukocytes
    - ↑ Transaminases (ALT, AST)
    - ABG/VBG
      - Metabolic acidosis
  - Urine studies –
    - Myoglobinuria

- Other investigations to consider:
  - Neuroimaging
  - CSF analysis
  - EEG
  - Lithium level
  - UDS

NMS is a diagnosis of exclusion

DSM-V CRITERIA

- Must fulfil all **yellow** criteria AND at least two **green** criteria

Exposure to anti-dopaminergic agent

Mental status change (encephalopathy)

- Altered level of consciousness
- Delirium
- Mutism

Parkinsonism

- Muscle rigidity (lead-pipe rigidity)
- Akinesia
- Tremor
- Hyporeflexia

Hyperthermia

Autonomic instability

- Tachycardia, dysrhythmias, diaphoresis
- Labile blood pressure
- Tachypnea
- Incontinence

Laboratory studies

- ↑ ↑ Creatine kinase
- ↑ ↑ Leukocytes

DIFFERENTIAL DIAGNOSES*

- Toxic or pharmacological:
  - **Serotonin syndrome**
  - **Anticholinergic toxicity**
  - **Malignant hyperthermia**
  - Dopamine agonist withdrawal syndrome (DAWS)
  - Substance abuse (sympathomimetics, hallucinogens)
  - Withdrawal syndromes (alcohol, benzodiazepines)
  - Syndrome of irreversible lithium-effectuated neurotoxicity (SILENT)
- Infectious:
  - Meningitis/encephalitis or brain abscess
  - Sepsis
- Neurological or psychiatric:
  - Agitated delirium
  - Malignant catatonia
  - Non-convulsive status epilepticus
  - Structural lesions
  - Parkinsonian hyperpyrexia syndrome (PHS)
- Endocrine:
  - Thyrotoxicosis
  - Pheochromocytoma
- Environmental:
  - Heatstroke

*List is not exhaustive

OTHER DRUG-INDUCED HYPERTHERMIAS

Serotonin syndrome

- Caused by serotonin overactivity due to use of serotonergic drugs
  - Rapid onset (<24 h)
- Clinical features include:
  - Hyperthermia
  - Neuromuscular excitability e.g. rigidity, hyperreflexia, myoclonus
  - GI symptoms
  - Autonomic dysfunction
  - Altered mental state
  - Rhabdomyolysis
- Usually resolves within 24 hours of serotonergic drug cessation

OTHER DRUG-INDUCED HYPERTHERMIAS

Anticholinergic toxicity

- Syndrome induced by anticholinergic agent overdose e.g. atropine, TCAs, clozapine
  - Rapid onset (<24 h)
- Clinical features include:
  - Hyperthermia
  - Dry mouth, eyes, skin
  - Tachycardia, arrhythmias
  - Altered mental state

OTHER DRUG-INDUCED HYPERTHERMIAS

Malignant hyperthermia

- Uncontrollable skeletal muscle contractions that lead to a hypercatabolic state and hyperthermia induced by anesthesic agents e.g volatile anaesthetics, suxamethonium
  - Rapid onset (<24 h)
- Clinical features include:
  - Hyperthermia
  - Generalized muscle rigidity (particularly masseter rigidity)
  - Tachycardia
  - Tachypnea, cyanosis
  - Rhabdomyolysis

MANAGMENT

- NMS is a neurologic emergency
- Prompt diagnosis and treatment is crucial to preventing significant morbidity or death
- **Discontinue the causative agent**
- Consider multidisciplinary team input

TREATMENT

- Supportive therapy:
  - Consider ICU admission for close monitoring
  - Antiarrhythmic agents and mechanical ventilation as needed
  - Aggressive cooling
  - Correction of volume deficits and electrolyte imbalances

- Pharmacotherapy:
  - Oral bromocriptine (dopamine agonist) or via NGT → reverses hypodopaminergic state
  - Oral or IV dantrolene (muscle relaxant) → reduces rigidity and hyperthermia
  - Benzodiazepine → treats catatonic symptoms

- ECT may be effective in refractory cases[5]

PROGNOSIS

- Typically self-limiting once anti-dopaminergic agents ceased
  - Mean recovery time after drug discontinuation is 2-14 days[6]
  - Delayed treatment may result in residual catatonia, parkinsonism, renal or cardiopulmonary complications

- Mortality <10%[4, 6]
  - Death may result from cardiac arrhythmias, disseminated intravascular coagulation, respiratory failure or renal failure

- Most patients may be restarted on neuroleptic medication at a minimum of 2 weeks post-resolution of symptoms
  - Monitor for recurrent symptoms
  - Start with low doses and slowly titrate up
  - Avoid higher potency agents
  - Avoid use in conjunction with lithium
  - Avoid dehydration

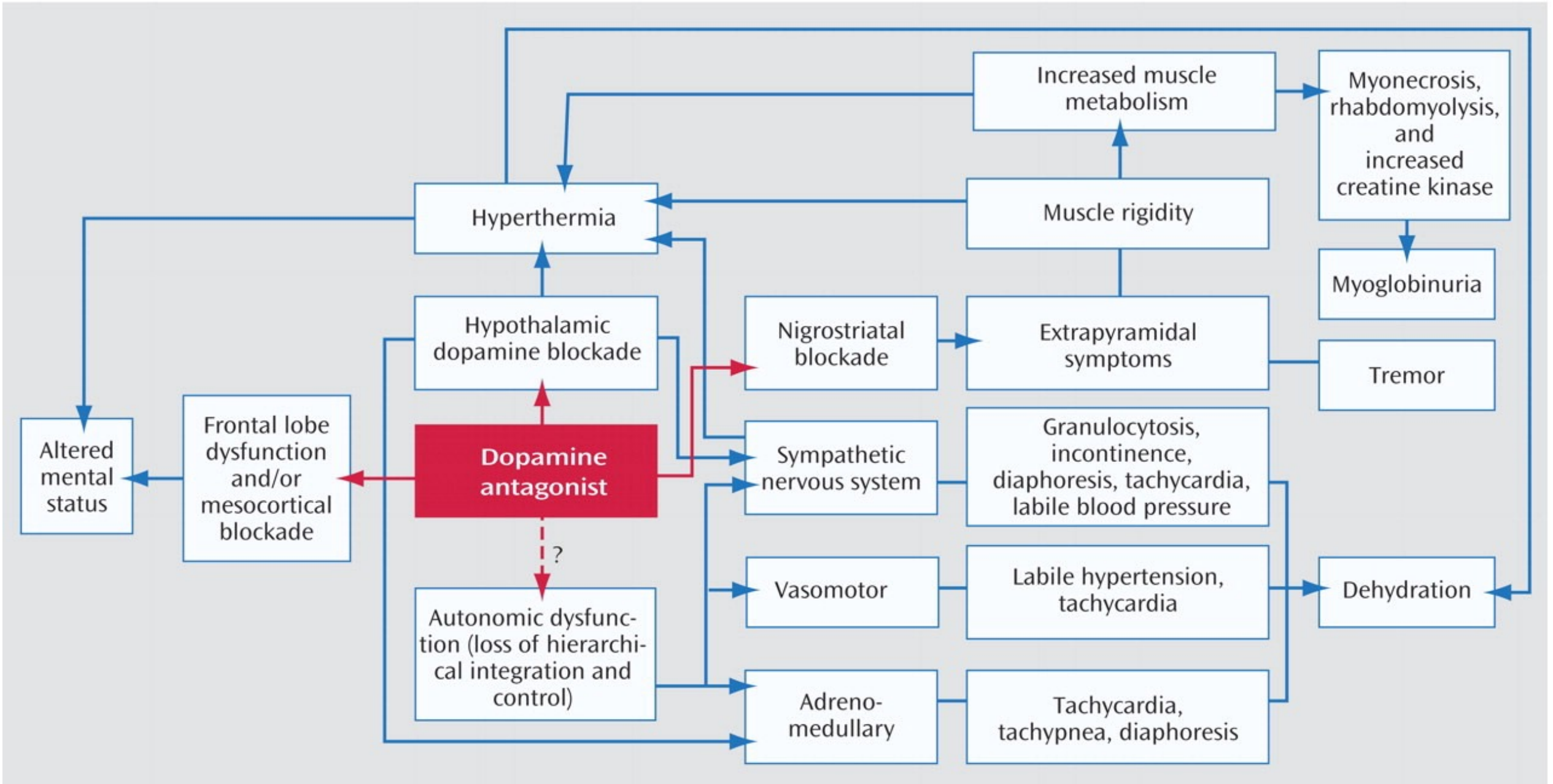


Figure 1. Simplified pathophysiology of NMS. Sourced from American Journal of Psychiatry[4]

Characteristics		Neuroleptic malignant syndrome	Serotonin syndrome	Malignant hyperthermia	Anticholinergic toxicity
Causative agents		Antidopaminergic agents e.g. haloperidol, chlorpromazine	Serotinergic drugs e.g. SSRIs, MAOIs, TCAs, MDMA, triptans	Volatile anesthetics e.g. halothane, sevoflurane Succinylcholine	Anticholinergic agents e.g. atropine TCAs Antipsychotics e.g. clozapine, quetiapine 1st gen antihistamines e.g. promethazine
Onset		Days to weeks	<24 h	Minutes – 24 h	<24 h
Clinical features	Autonomic dysfunction	Hyperthermia Hypertension Tachycardia Tachypnea Mydriasis	Hyperthermia Hypertension Diarrhea Mydriasis Diaphoresis	Hyperthermia Tachypnea Hypertension Tachycardia Mottled skin	Hyperthermia Tachycardia, arrhythmias Dry mouth, dry skin Mydriasis Urinary retention Constipation
	Changes in neuromuscular activity	Hypoactivity (parkinsonism) Hyporeflexia Tremor Lead-pipe rigidity	Hyperactivity Hyperreflexia Tremor Clonus Hypertonia	Masseter muscle contracture Generalized muscular rigidity	None (normal reflexes and tone)
	Altered mental state	Confusion delirium	Agitation Coma	Confusion possible	Delirium possible
Laboratory findings		↑ CK ↑ WCC Myoglobinuria	Non-specific	↑ End tidal CO_2 Metabolic acidosis Hyperkalemia	Non-specific
Treatment		Discontinuation of causative drug Bromocriptine (dopamine agonist) Dantrolene (muscle relaxant) Benzodiazepine	Discontinuation of serotonergic drugs Benzodiazepines Cyproheptadine	Discontinuation of causative drugs Dantrolene Cooling	Phygostigmine

Table 1. Characteristics of differential diagnoses for drug-induced hyperthermia

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