Neuroleptic Malignant Syndrome

Overview

- **The neuroleptic malignant syndrome (NMS) is a rare, but life-threatening, idiosyncratic reaction to a neuroleptic medication.**
- **characterized by:**
  - **Fever.**
  - **muscular rigidity.**
  - **altered mental status.**
  - **autonomic dysfunction.**

Pathophysiology

- The cause of NMS is unknown . Current theories are limited in their ability to explain all clinical manifestations of NMS .

Pathophysiology

- The mechanism is thought to depend on decreased levels of dopamine activity due to:

  - Dopamine receptor blockade.
  - Genetically reduced function of dopamine receptor D_2.

Pathophysiology

- Disrupted modulation of the sympathetic nervous system; causing increased muscle tone, ineffective heat dissipation, labile blood pressure & heart rate.

Pathophysiology

- Some say that rigidity & muscle damage is an effect from direct changes in muscle mitochondrial function.
- Familial clusters suggest a genetic predisposition.

EPIDEMIOLOGY

- Incidence rate for neuroleptic malignant syndrome (NMS) range from 0.02 to 3 percent among patients taking neuroleptic agents.
- Most patients with NMS are **young** adults, the syndrome has been described in all age groups. Age not a risk factor .
- In most studies , **men** outnumber women two folds.

Agents have been associated with NMS:

- NMS is most often seen with the **typical** high potency neuroleptic agents (eg . haloperidol , fluphenazine) .
- Every class of neuroleptic drug has been implicated, including the low potency (eg , chloropromazine), & the newer **atypical** antipsychotic drug (eg , clonzapine , risperidone , olanzapine).

Agents have been associated with NMS:

- has also been associated with **non-neuroleptic** agents that block central dopamine pathways such as metoclopramide, amoxapine , promethazine and lithium.

Agents have been associated with NMS:

- NMS can occur after a single dose or after treatment with the same agent at the same dose for many years.
- It is not a dose dependent phenomenon- i.e. idiosyncratic , but higher dose are a risk factor.

Agents have been associated with NMS:

- Case control studies implicate **recent or rapid dose escalation** , a **switch from one agent to another** , and **parenteral administration** as risk factors .

Agents have been associated with NMS:

- Other commonly listed risk factor :
  - concomitant use of lithium or other psychotropic drug.
  - higher potency agent.
  - depot formulations.
  - comorbid substance abuse.
  - neurologic disease.
  - acute medical illness (including trauma , surgery , and infection).
  - dehydration. (? Risk factor vs Early complication of NMS).

Agents have been associated with NMS:

- Antiparkinson medication withdrawal : NMS is also seen in patients treated for parkinsonism in the sitting of withdrawal of l-dopa or dopamine agonist therapy , as well as with dose reductions and a switch from one agent to another .

Clinical manifestations

- NMS is defined by a tetrad of distinctive clinical features : **fever** , **rigidity** , **mental status changes** , and **autonomic instability** .
- Typically evolves over one to three days .

Clinical manifestations

- Mental status change is the initial symptom in most patients, takes the form of agitated delirium with confusion.
- Muscular rigidity is generalized, characterized by lead pipe rigidity.

Clinical manifestations

- Hyperthermia is a defining symptom according to many diagnostic criteria . Temperatures of more than 38 c are typical, but even higher temperatures , greater than 40 c, are common.
- Autonomic instability taking the form of tachycardia & tachypnea. Dysrhythmia may occur. Diaphoresis is often perfuse.

Differential diagnosis

- Can be broadly defined in two categories; those that are related to NMS and those unrelated to NMS but commonly **considered** in the differential diagnosis.
- **Related** disorders: share common features, distinguished if only by the implicated drug.

Differential diagnosis

- 1- serotonin syndrome: the most common related disorder. Usually caused by SSRI & has similar presentation of NMS. Has symptoms not present in NMS: shivering, hyperreflexia, myoclonus, vomiting & diarrea.

Differential diagnosis

- 2- Malignant hyperthermia: a rare genetic disorder, occur with the use of potent halogenated inhalational anesthesia & succinylcholine.
  - It's clinical manifestations are more fulminant than NMS.

Differential diagnosis

- 3- Malignant catatonia: most problematic in the DDx. . In this syndrome, there is usually a behavioral prodrome of some weeks; characterized by psychosis, agitation & catatonic excitement. Both syndromes may overlap.

Differential diagnosis

- 4- Others:
  - Withdrawal of intrathecal baclofen therapy (skeletal muscle relaxant).
  - Acute intoxication of recreational drugs esp. cocaine & ecstasy. Rigidity is not common in these cases.

Differential diagnosis

- **Unrelated** disorders: neurological & medical disorders that should be considered. Symptoms can overlap esp. in those with extrapyramidal side effects.
  - 1- Central nervous system infection (eg, meningitis, encephalitis).
  - 2- Systemic infection (eg, pneumonia , sepsis).

Differential diagnosis

- 3- Seizures.
- 4- Acute hydrocephalus.
- 5- Acute spinal cord injury.
- 6- Heat stroke.
- 7- Acute dystonia.
- 8- Tetanus.
- 9- Central nervous system vasculitis.
- 10- Thyrotoxicosis.
- 11- Withdrawal states.
- 12- Acute porphyria.

Diagnostic testing

- Laboratory abnormalities:
  - Elevated serum CK , typically more than 1000 IU/l .
  - Leukocytosis, WBC typically 10,000 to 40,000
  - Mild elevation of LDH, Alkaline phosphatase, and liver transaminases are common.

Diagnostic testing

- Electrolyte abnormality: hypocalcemia, hypomagnesemia, hypo and hypernatremia, hyperkalemia and metabolic acidosis are frequently observed .

Diagnostic testing

- Myoglobinuric acute renal failure can result from rhabdomyolysis.
- A low serum iron concentration.

Treatment

- **Stop causative agent**: the single most important treatment.
- **Supportive care**: the need for aggressive and supportive care in NMS is essential and uncontroversial.

Treatment

- Admission to ICU is required.
- Maintain cardiorespiratory stability.
- Maintain euvolemic stability using IVFs.
- Lower fever using cooling blankets.
- Lower BP if markedly elevated.
- Prescribe heparin to prevent DVT.
- Use benzodiazepines to control agitation, if necessary.

Treatment

- Specific treatments
  - Dantrolene: is direct acting skeletal muscle relaxant and is effective in treating malignant hyperthermia.
  - Bromocripitine: a dopamine agonist , is prescribed to restore lost dopaminergic tone .
  - Amantadine: dopaminergic & anticholinergic effects. Used alternative to bromocriptine.

Treatment

- Electroconvulsive (ECT) therapy is generally reserved for patients not responding to other treatments or in whom nonpharmacologic psychotropic treatment is needed .

Prognosis

- Most episode resolve within two weak .
- Mortality rates for NMS are 10 to 20%.
- Disease severity and the occurrence of medical complication are the strongest predictors of mortality .

- **Restarting antipsychotic** ,the following guidelines may minimize risk of NMS recurrence :
- .Wait at least two weeks before resuming therapy .

  . Use lower rather than higher potency agent .

  . Start with low doses and titrate upward slowly.

  .Avoid concomitant lithium .

  .Avoid dehydration .

NMS and SGAs

- Case reports have made it clear that SGAs like first generation antipsychotic can precipitate this life threatening neurological emergency .
- Clozapine (leponex) , NMS occurred sooner , the presentation ranged from typical with high CPK to mild with no rigidity and mild or no CPK elevation .
- Clozapine has been used to treat patient with a history of NMS who experience psychotic relapse.
- Risperidone , more frequently, NMS occur from hours to months , atypical presentation especially hyponatremia .
- Olanzapine , rare , onset from within 8 hours to after 2and half years of stable olanzapine , atypical presentation include normal CPK, absence of rigidity , high Na

- Before we write a prescription , we review the diagnosis, the known evidence, and our own experience , then we discuss the risks and benefits with the patients .
- If he chooses to fill the prescription , we are responsible for the outcome .

Thank you