Neuroleptic Malignant Syndrome

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Objectives

- Identifying Neuroleptic Malignant Syndrome
- Pathophysiology of Neuroleptic Malignant Syndrome
- Treatment of Neuroleptic Malignant Syndrome
- Legal aspects

Introduction

- Life threatening and potentially fatal.
- Idiosyncratic reaction to a neuroleptic medication.
- Delay and Colleagues
  - ‘akinetic hypertonic syndrome’
  - After introduction of neuroleptics in 1960
  - Typical and Atypical Antipsychotics
Associated Medications

- Most often seen with the typical high potency neuroleptic agents
- Reported also with:
  - low potency neuroleptic agents
  - atypical antipsychotic agents
  - antiemetic agents
- Antiparkinson medication withdrawal

Epidemiology

- Incidence
  
  Agency for Healthcare Research and Quality
  
  - 2000 – 2075 cases
  - 2001 – 2444 cases
  - 2002 – 1835 cases

Epidemiology

- Most frequently older antipsychotics
- Duration of treatment
- No geographic variation
- No racial variation
- Higher in males
- Less than 40 years of age
- Elderly and children
- 0.02 to 2.4 percent

Risk factors

- Keck and associates
- Pre-morbid Psychomotor agitation
  
  - Higher doses of neuroleptics with greater rates of dose increase
  
  - Higher number of intramuscular injections
- Concurrent use of lithium
**Risk Factors**
- Simultaneous use of 2 or more neuroleptics
- Encephalitis, AIDS increase susceptibility
- Dehydration
- High serum creatinine kinase
- Iron deficiency

**Mortality**
- 10 – 20%
- Decreased over the past 2 decades
- Maybe due to the awareness of the syndrome
- Higher mortality with medical complications and substance abuse

**Neuroleptic Malignant Syndrome**
- Detection of Suspected Neuroleptic Malignant Syndrome DVD/VHS Trailer

**Pathogenesis**
- 2 Major Theories.
  - Central dopamine blockade theory.
  - Neuroleptic induced muscle toxicity.
Central Dopamine Blockade Theory
- Thermoregulation
- Suggested by Henderson and Wooten
- Hypothalamus
  - Impaired heat dissipation
- Corpus Striatum
  - Muscle rigidity
- Spinal cord
  - Autonomic disturbances
- Low CSF dopamine metabolite

Dopamine Activity

Pathophysiology

Neuroleptic Induced Muscle Toxicity
- Calcium ion transport
- Increased contractility
- Hyperthermia
- Muscle cell breakdown
- Dantrolene
Genetics
- Familial clusters
- D2 receptor gene
- Reduced function of dopamine receptors
- Inherited changes

Clinical Manifestations
- Mental status change
  - 82% of patients
- Muscular rigidity
  - Lead pipe rigidity
- Hyperthermia
  - 87% of patients
- Autonomic instability
  - 88% of patients

Atypical Manifestations
- Atypical antipsychotics
- Conventional antipsychotics
- Varied presentation
- DSM V

Criteria A
- Development of severe muscle rigidity
- Development of elevated temperature
- Associated with neuroleptic medication use
Criteria B

- Two or more of the following:
  1. diaphoresis
  2. dysphagia
  3. tremor
  4. incontinence
  5. changes in the level of consciousness ranging from confusion to coma
  6. mutism
  7. tachycardia
  8. elevated or labile blood pressure
  9. leukocytosis
  10. Laboratory evidence of muscle injury (e.g., Elevated CPK)

Criteria C

- The symptoms in Criteria A and B are not due to another substance (e.g., Phencyclidine) or a neurological or other general medical condition (e.g., Viral encephalitis).

Criteria D

- The symptoms in Criteria A and B are not better accounted for by a mental disorder (e.g., Mood disorder with catatonic features).

Dysautonomic syndromes

- Serotonin syndrome
- Malignant hyperthermia
- Malignant catatonia
- Central anticholinergic syndrome and other drug related syndromes
**Serotonin Syndrome**
- Use of Serotonin Specific Reuptake Inhibitors
- Shivering
- Hyperreflexia
- Myoclonus
- Ataxia
- GI effects

**NMS vs. Serotonin Syndrome**
- Detailed history of medication use
- Medication dose adjustment
- Symptom onset
- Neuromuscular
- Rhabdomyolysis
- Metabolic Acidosis

**Malignant Hyperthermia**
- Rare genetic disorder
- Associated with anesthetic agents
- Hyperthermia
- Muscle rigidity
- Dysautonomia
- Muscle contracture testing

**Malignant Catatonia**
- Behavioral prodrome
- Psychosis, agitation, catatonic excitement
  - Dystonic posturing, waxy flexibility, stereotyped repetitive movements
- Impossible to differentiate in 22% of patients
- Laboratory values are typically normal
Catatonia

- http://www.youtube.com/watch?v=zAEi-Jvndms

Anticholinergic Syndrome

- Dry skin, decreased sweating, mydriasis, dry mouth
- Less severe elevated body temperature and encephalopathy
- Creatinine kinase levels not elevated
- Diaphoresis and rigidity are absent

Other Drugs

- Cocaine and ecstasy
- Increased physical exertion
- Rigidity is not common

Differential Diagnosis

<table>
<thead>
<tr>
<th>Competing diagnosis</th>
<th>Distinguishing clinical features of the competing diagnosis</th>
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<tbody>
<tr>
<td>Malignant hypothermia</td>
<td>Occurs after general anesthesia</td>
</tr>
<tr>
<td>Lethal catatonia</td>
<td>Similar symptoms without neurologic examination</td>
</tr>
<tr>
<td>Heat stroke</td>
<td>Hypothermia, absence of rigidity</td>
</tr>
<tr>
<td>Severe extrapyramidal symptoms and Parkinson’s disease</td>
<td>Absence of fever, tachycardia, autonomic changes</td>
</tr>
<tr>
<td>Central nervous system infection</td>
<td>Seizures more likely, significant abnormalities in encephalopathy</td>
</tr>
<tr>
<td>Allergic drug reactions</td>
<td>Rashes, urticaria, wheezing, monoclonal</td>
</tr>
<tr>
<td>Toxic-extrinsic parkinson’s toxicity</td>
<td>Absence of fever, low creatinine phosphate</td>
</tr>
<tr>
<td>Anticholinergic delirium</td>
<td>Absence of rigidity, low creatinine</td>
</tr>
<tr>
<td>Systemic infection plus severe extrapyramidal symptoms</td>
<td>May appear identical to neurologic malignant syndrome</td>
</tr>
</tbody>
</table>
**Investigations**
- Complete blood count (CBC)
- Blood cultures
- Comprehensive metabolic profile
- Creatinine kinase level
- Urine myoglobin level
- Arterial blood gas (ABG) level
- INR
- Serum and urine drug screening (e.g., salicylates, cocaine, amphetamines)

**Imaging**
- CXR
- CT Head
- Lumbar Puncture

**Laboratory Abnormalities**
- Elevated serum CK
- Leukocytosis
- Liver transaminases
- Acute renal failure

**Histology**
- Muscle Biopsy
  - Controversial
  - Grossly swollen
  - Edematous
  - Necrosis
**Histology**

![Histology Image]

**NMS Complications**
- Rhabdomyolysis
- Acute renal failure
- Thromboembolism
- Acute respiratory failure
- Seizures
- DIC
- Hepatic failure
- Sepsis

**Prognosis**
- Resolution in 2 weeks
- Prolonged course
  - Depot antipsychotics
  - Structural brain disease
- Sequelae

**Management**
- Prompt recognition
- Immediate discontinuation of the neuroleptic
- Intensive supportive care and medical monitoring
- Treatment of comorbid medical illness
Supportive Measures

- Reduce body temperature.
- Treat suspected or secondary infections with empiric antibiotics.
- Consider intubation for patients with excessive salivation, swallowing dysfunction, coma, hypoxemia, acidosis, and severe rigidity with hyperthermia.
- Aggressive hydration
- Hemodynamic monitoring.
- Sedate the patient.

Pharmacotherapy

- Rapid peripheral muscle relaxation
- Dantrolene
- Dopamine agonists
- Combined therapy

Dantrolene

- Muscle relaxant
- Inhibits calcium ion release
- Recommended for severe hyperthermia
  - 25 mg/d PO initially
  - Gradually increase to tid/qid
  - Not to exceed 400 mg/d

Dopamine Agonists

- Bromocriptine
- Amantadine
- Levodopa and carbidopa
ECT and NMS

- Alternative to oral treatment
- Reasonable treatment option
- 6-10 treatments
- Hydration

Post NMS Neuroleptic Use

- Wait at least 2 weeks
- Use lower potency antipsychotics
- Start low and go slow with titration
- Avoid concomitant lithium use
- Avoid dehydration
- Monitor for NMS

NMS Sequelae

- Cerebellar neuronal degeneration
- Lithium
- Dysarthria
- Difficulties comprehending commands
- Attention problems
- Abnormalities in her muscle tone, power, reflexes, gait, coordination and sensory function
- Cerebellar gait ataxia

NMS in Children and Adolescents

- Dr. Neuhut et al
- Published cases over an 18 year period
- Increased creatinine kinase, fever, tachycardia, rigidity, altered mental state
- Prompt management
- NMS symptoms resolved
- No reported deaths
Legal Aspects

- Use of dantrolene or bromocriptine
- Risk factors
- Informed consent
- Psychoeducation

Legal Aspects

- Discontinue neuroleptic promptly.
- Seek appropriate consultation.
- Transfer to higher level of care.
- Document differential diagnosis.
- Document treatment plan.
- Inform the family.

Resources

- Neuroleptic Malignant Syndrome Information Services
  - NMSIS
  - 888-667-8367
  - www.nmsis.org

Resources

- National Organization for Rare Disorders
  - (NORD)
  - orphan@rarediseases.org
  - www.rarediseases.org
  - Tel: 203-744-0100
References

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