Neuroleptic Malignant Syndrome: A Case Presentation

Janel Liane Bernardo Cala
PGY1 Pharmacy Resident
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Neuroleptic Malignant Syndrome

- Infrequent (0.02% – 3% neuroleptic use), life threatening
- Most often associated with high potency neuroleptics, but all classes have been implicated
  - including atypical APs and antiemetics (metoclopramide, promethazine)
- More likely to develop following initiation of neuroleptic therapy or an increase in the dose of drug

- Decreased dopamine activity in CNS
  - D2 receptor Blockade
  - Decreased Dopamine availability

Onset: can be hours, but mostly 4-14 days after initiation of therapy
# Antipsychotics

<table>
<thead>
<tr>
<th>Low Potency</th>
<th>High Potency</th>
<th>Newer Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Haloperidol</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Perphenazine</td>
<td>Olanzapine</td>
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<tr>
<td></td>
<td>Pimozide</td>
<td>Quetiapine</td>
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<td></td>
<td>Fluphenazine</td>
<td>Aripiprazole</td>
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<td></td>
<td></td>
<td>Ziprasidone</td>
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<tr>
<td><strong>Less EPS</strong></td>
<td><strong>More EPS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>More Anticholinergic</strong></td>
<td><strong>Less Anticholinergic</strong></td>
<td></td>
</tr>
<tr>
<td>Typical Antipsychotics</td>
<td>Atypical Antipsychotics</td>
<td>Antiemetics</td>
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</tr>
<tr>
<td>Chlorpromazine</td>
<td>Aripiprazole</td>
<td>Droperidol</td>
</tr>
<tr>
<td>Chlorprothixene</td>
<td>Clozapine</td>
<td>Metoclopramide</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>Olanzapine</td>
<td>Prochlorperazine</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Quetiapine</td>
<td>Promethazine</td>
</tr>
<tr>
<td>Loxapine</td>
<td>Risperidone</td>
<td></td>
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<tr>
<td>Mesoridazine</td>
<td>Ziprasidone</td>
<td></td>
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<tr>
<td>Molindone</td>
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<td>Perphenazine</td>
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<tr>
<td>Thiothixene</td>
<td></td>
<td></td>
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<tr>
<td>Trifluoperazine</td>
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</tr>
</tbody>
</table>

NMS: neuroleptic malignant syndrome.
Source: Reference 20.
<table>
<thead>
<tr>
<th>Pathogenesis of neuroleptic malignant syndrome (NMS) (secondary to drugs), at cellular level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Presynaptic</strong></td>
</tr>
<tr>
<td>Dopamine (DA) depleters</td>
</tr>
<tr>
<td>Reduced DA precursor</td>
</tr>
<tr>
<td><strong>Synaptic</strong></td>
</tr>
<tr>
<td>Altered DA metabolism</td>
</tr>
<tr>
<td>Altered DA reuptake</td>
</tr>
<tr>
<td><strong>Postsynaptic</strong></td>
</tr>
<tr>
<td>D2 receptor blockade</td>
</tr>
<tr>
<td>Reduced postsynaptic stimulation</td>
</tr>
</tbody>
</table>
Clinical Features

- Hyperthermia
- Motor Symptoms
- Autonomic Instability
- Altered Mental Status
- Elevated CK
Risk Factors

- Higher doses of neuroleptics
- Greater neuroleptic dose increments over short period (<5 days)
- Simultaneous use of ≥2 neuroleptic drugs
- Parenteral administration of neuroleptics (especially IM depot)
- Male gender
- Dehydration
### TABLE 3 | The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for diagnosis of neuroleptic malignant syndrome (NMS)

- The development of severe muscle rigidity and elevated temperature associated with the use of antipsychotic medication.
- Two or more of the following:
  - Diaphoresis
  - Elevated or labile blood pressure (BP)
  - Tachycardia
  - Incontinence
  - Dysphagia
  - Mutism
  - Tremor
  - Changes in the level of consciousness ranging from confusion to coma
  - Leukocytosis
  - Laboratory evidence of muscle injury [e.g. elevated creatinine phosphokinase (CK)]
  - Diaphoresis
  - Elevated BP
  - Tachycardia

- The symptoms in Criteria A and B are not due to another substance (e.g. phencyclidine), neurological or other medical conditions (e.g. viral encephalitis).
- The symptoms in Criteria A and B are not better accounted for by a mental disorder (e.g. mood disorder with catatonic features).

### TABLE 4 | Levenson’s clinical criteria for diagnosis of neuroleptic malignant syndrome (NMS)

<table>
<thead>
<tr>
<th>Category</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>Fever, rigidity, elevated creatinine phosphokinase concentration</td>
</tr>
<tr>
<td>Minor</td>
<td>Tachycardia, abnormal arterial pressure, tachycardia, altered consciousness, diaphoresis, leukocytosis</td>
</tr>
</tbody>
</table>

Source: Data from Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). Washington, DC: American Psychiatry Association; 1994
Complications

- Dehydration
- Electrolyte Imbalances
- Acute renal failure 2/2 rhabdomyolysis
- Cardiac arrhythmias
- Respiratory failure 2/2 chest wall rigidity, aspiration
- DVT
- Seizures 2/2 hyperthermia, electrolyte disturbances
Management

- Supportive Care
- Pharmacotherapy
- Electroconvulsive Therapy
Supportive Care

- Discontinue neuroleptic agent or precipitating drug
- Maintain cardiorespiratory stability
  - +/- Mechanical Ventilation
  - +/- Antiarrhythmics
- IV hydration
  - +/- high volume fluids
  - Urine alkalinization (IV NaHCO3)
- Lower temperature
- Lower BP (Clonidine)
- DVT ppx
- Control agitation (BZDs)
<table>
<thead>
<tr>
<th>Category</th>
<th>Bromocriptine</th>
<th>Dantrolene</th>
<th>Amantadine</th>
<th>Levodopa and carbidopa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Central dopamine (DA) agonist</td>
<td>Skeletal muscle relaxation via inhibition of calcium release from sarcoplasmic reticulum</td>
<td>Release DA from dopaminergic terminals and other central sites</td>
<td>Dopamine agonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Secondary to muscle relaxation; it may decrease body temperature, oxygen consumption, heart rate and respiratory rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>Oral: 2.5–10 mg/d four times a day with increments of 2.5 mg tid every 24 hours until a response is seen or up to 60 mg/d</td>
<td>Oral: 50–200 mg/d</td>
<td>100–300 mg bd</td>
<td>25–250 mg tds or qid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intravenous: 2–3 mg/kg/d up to a dose of 10 mg/kg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Dose-limiting hypotension, psychosis, nausea and so forth</td>
<td>Hepatotoxicity (especially with doses &gt; 10 mg/kg/d)</td>
<td>Hepatotoxicity, uncontrolled psychosis, seizures</td>
<td>MI, arrhythmia, asthma, peptic ulcer, dyskinesia</td>
</tr>
</tbody>
</table>
Electroconvulsive Therapy

- Done under general anesthesia
- Small electric currents are passed through the brain
- Triggers a brief seizure → changes in brain chemistry → reverse illness
- Facilitates brain DA activity (?)
- Improves
  - Fever
  - Sweating
  - Level of consciousness
- For severe and refractory NMS (>48hr)
CASE PRESENTATION

Neuroleptic Malignant Syndrome (NMS)

- I was started on an Antipsychotic 2-10 days ago.

Differential DX:
- Serotonin Syndrome
- Anticholinergic

NMS Mneumonic
- Fever
- Ams
- Leukocytosis
- Tremors
- Elevated CPK
- Rigidity

NMS Tetrad
- AMS
- Temp
- Autonomic
- Instability

“In Parkinson’s disease, when a dopaminergic drug is stopped, the patient can present just like NMS.”
WK, 35M, presented to MCH ER for Fever, AMS

Per Mom: mental status worse this morning, “speaking like a crazy man”

PMH: Psychosis

Allergy: NKDA

Recent admission in MMH 2/2 Haldol overdose

Home Meds: ergocalciferol 8000 IU/mL; olanzapine 2.5mg qd
HR 128, RR 25, BP 189/101, Tmax 104

Na 166, K 3.4, Cl 128; CO2 21; BUN 27; SCr 1.5
Sugar 873, Lactate 4, WBC 11.6
AG 22, Osm 372, pH 7.38, HCO3 20

CXR suggestive of PNA
UA clean; (+) ketones, protein
LP not done, mother refused
Drug levels negative (salicylate, EtOH, BZD, opioid, APAP)

Initial Diagnosis: DKA, Pneumonia (both managed accordingly), new onset DM (A1C 11.9)
Home meds restarted
<table>
<thead>
<tr>
<th>Lab View</th>
<th>08/19/17 00:00 - 23:59 CDT</th>
<th>08/18/17 00:00 - 23:59 CDT</th>
<th>08/17/17 00:00 - 23:59 CDT</th>
<th>08/16/17 00:00 - 23:59 CDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine Lvl</td>
<td>1.4 (H)</td>
<td>1.8 - 2.1 [2][2][H][I]</td>
<td>1.4 - 2.0 [2][2][H][I]</td>
<td>1.4 - 1.5 [2][2][H][I]</td>
</tr>
<tr>
<td>Sodium Level</td>
<td>139</td>
<td>139 - 145 [2][2][H][I]</td>
<td>159 - 162 [2][2][I]</td>
<td>162 - 166 [2][2][I]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CBC and Differential</th>
<th>WBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/22/17 00:00 - 23:59 CDT</td>
<td>5.6</td>
</tr>
<tr>
<td>08/21/17 00:00 - 23:59 CDT</td>
<td>4.8</td>
</tr>
<tr>
<td>08/20/17 00:00 - 23:59 CDT</td>
<td>5.8</td>
</tr>
<tr>
<td>08/19/17 00:00 - 23:59 CDT</td>
<td>7.0</td>
</tr>
<tr>
<td>08/18/17 00:00 - 23:59 CDT</td>
<td>9.6</td>
</tr>
<tr>
<td>08/17/17 00:00 - 23:59 CDT</td>
<td>7.6</td>
</tr>
<tr>
<td>08/16/17 00:00 - 23:59 CDT</td>
<td>11.6 (H)</td>
</tr>
</tbody>
</table>
Over the course of a few days,
- DKA resolved
- electrolytes normalized
- WBC trended down quickly
- Cultures were unremarkable
- Still spiking high grade fever despite being on adequate antibiotic therapy
- Vitals were unstable
- Patient would burst out nonsensical statements intermittently
- Disoriented to time and place
- Muscle stiffness is seen; Left hand contracture is noted
- No facial droop seen
ID was consulted; Pancultures were sent

Per ID fever’s etiology is unclear; suggested to take CK levels

<table>
<thead>
<tr>
<th>CK</th>
<th>2,743 (H)</th>
<th>&gt;4267 * (H)</th>
<th>7,602 * (H)</th>
<th>8,486 * (H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U Myoglobin-ARUP</td>
<td></td>
<td></td>
<td></td>
<td>82 * (H)</td>
</tr>
</tbody>
</table>

Olanzapine was discontinued
Bromocriptine 2.5 mg TID was started
Cooling Blanket, APAP prn
Pyrexia started resolving, CK started decreasing, muscle rigidity improving
Psych consult
Transfer out
Olanzapine

- Atypical antipsychotic
- High affinity to 5HT2A/2C; Dopamine D1-D4, Muscarinic 11-6, Histamine H1 and Adrenergic α1
- MOA: 5HT2 + D2 antagonism
- T1/2: 21-54 hr (IR); 30 d (ER)
- Vd: 1000 L
- Adverse effects: orthostatic hypotension, EPS, hypertriglyceridemia, weight gain, hyperglycemia
- 5-10 mg/d; titrate in increments of 5mg/day at intervals > 1 week; MAX: 20mg/day
Discussion

- Most cases resolve within 2 weeks, usually 7-11 days
- Cases of >6 months motor symptoms are reported
- Risk factors for prolonged cause
  - IM depot antipsychotic injections
  - Structural brain disease
- Most patients recover without neurologic sequelae
- Patient restarted on neuroleptic agents may or may not have NMS recurrence
Restarting Neuroleptics

- Risk factors for recurrence:
  - Early resumption of neuroleptic therapy
  - Use of high potency drugs
  - Parenteral neuroleptics
  - Concomitant use of lithium

To restart neuroleptic therapy,
- Wait at least 2 weeks
- Use Low potency
- Start with low doses and titrate slowly
- Avoid lithium
- Avoid dehydration
- Carefully monitor for NMS symptoms
References