Catatonia, NMS, and Serotonin Syndrome

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## Disclosure: Christopher Celano, MD

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D – Relationship is considered directly relevant to the presentation
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Catatonia: How common is it?

• 7.8-9.0% prevalence rate
  – Highest rates in non-psychiatric (i.e., medical) settings and in patients undergoing ECT.
• 1.6-5.5% of all patients seen on psychiatry consultation service
  – Prevalence higher for older patients
• Up to 46% of cases may have etiology that is not primarily psychiatric

When are you called?

- Staff reports the patient is “Playing POSSUM”

- Perseveration (speech or behavior)
- Oppositionality to all requests
- Speech that trails off or is whispered
- Slowed response to questions or commands
- Undernourished (reports of decreased PO intake)
- Motionless but awake
Diagnosing Catatonia: DSM-5

DSM-5 requires 3 or more of the following:

- Catalepsy
- Waxy flexibility
- Stupor
- Agitation
- Mutism
- Negativism

- Posturing
- Mannerisms
- Stereotypies
- Grimacing
- Echolalia
- Echopraxia

American Psychiatric Association 2013
<table>
<thead>
<tr>
<th>Bush-Francis Rating Scale</th>
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<tr>
<td>• Excitement</td>
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<tr>
<td>• Immobility/stupor</td>
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<td>• Combativeness</td>
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<td>• Autonomic Abnormality</td>
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<td>• Impulsivity</td>
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<td>• Mutism</td>
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<td>• Staring</td>
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<td>• Posturing/catalepsy</td>
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<td>• Grimacing</td>
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<td>• Echopraxia/echolalia</td>
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<td>• Verbigeration</td>
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<tr>
<td>• Rigidity</td>
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<td>• Negativism</td>
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<tr>
<td>• Waxy flexibility</td>
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<tr>
<td>• Withdrawal</td>
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<tr>
<td>• Automatic Obedience</td>
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<td>• Mitgehen</td>
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<td>• Gegenhalten</td>
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<tr>
<td>• Ambitendency</td>
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<tr>
<td>• Grasp Reflex</td>
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<tr>
<td>• Perseveration</td>
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Bush 1996
Challenges with Diagnosis

• Clarifying specific symptoms can be difficult
  – Rigidity vs. gegenhalten vs. negativism
• Inconsistency between scales
• Symptoms occur on a spectrum
• Wide variety of manifestations
Prototypes of Catatonia

- The Distant Mute
  - Mutism, immobility, interpersonal withdrawal
  - Team may be concerned this is volitional
- The Waxy Stiff
  - Catalepsy, waxy flexibility, rigidity
  - Often identified by physicians; may misattribute to psychiatric illness
- The Broken Record
  - Echophenomena, verbigeration, hyperactivity
  - Often misdiagnosed as delirium
- The Stubborn Grouch
  - Negativism, repetitive movements, excitement
  - Medical workup often not completed due to lack of cooperation.
Pathophysiology of Catatonia

- Disruption in the tracts connecting the basal ganglia and the cortex, leading to relative hypodopaminergia.
  - Dorsolateral prefrontal and anterior cingulate / medial orbitofrontal → akinetic mutism, dysautonomia
  - Lateral orbitofrontal → imitative and repetitive behaviors
  - Supplementary motor / motor / posterior parietal → rigidity, initiation and termination of movement

- Hyperactivity of the supplementary motor area and presupplementary motor area → motor control, initiation and inhibition of movement

Fricchione 2008, Walther 2019
Pathophysiology of Catatonia

• GABA and serotonin may be involved
  – The dopaminergic projections in the brain are modulated by GABA-ergic and serotonergic neurons.
  – Benzodiazepines (GABA-A agonists) are helpful
  – GABA-B agonists (baclofen) are harmful and can induce catatonia
  – Serotonergic medications also may induce catatonic symptoms.

• Glutamate may also play a role
  – Anti-NMDA receptor encephalitis can cause catatonia.
  – NMDA receptor antagonists have been used as treatments in some cases.

Mann 1986, Rogers 2019
Evaluating Catatonic Patients

• Observe patient while trying to engage in conversation.
• Scratch your head in an exaggerated manner.
• Examine the patient’s arms for cogwheeling. Move the arms with alternating lighter and heavier force.
• Move patient’s arm into different positions and observe whether they remain in position.
• Ask the patient to extend his/her arms. Place one finger beneath each hand and try to raise it slowly after stating, “Do not let me raise your arms.”
Evaluating Catatonic Patients

• Extend your hand and state, “Do not shake my hand.”
• Reach into your pocket and state, “Stick out your tongue. I want to stick a pin in it.”
• Check for grasp reflex.
• Check the chart for reports from prior 24 hours. Check for PO intake, VS, and incident.
• Observe the patient indirectly daily to observe for other catatonic symptoms.
Potential Causes of Catatonia

• Medical Illness
  – Seizures
  – CNS structural damage
  – Encephalitis (e.g., anti-NMDA) or other CNS infection
  – SLE with or without cerebritis
  – Disulfiram
  – Phencyclidine
  – Neuroleptic exposure
  – Corticosteroid exposure
  – Porphyria
  – Post-partum state
  – Iron deficiency

• Psychiatric Illness
  – MDD
  – Bipolar Disorder
  – Psychotic disorders

Carroll 1994, Denysenko 2015
Workup for Catatonia

- Complete Blood Count, Comprehensive Metabolic Panel
- Creatine Kinase (to look for rhabdomyolysis)
- Iron studies
- Toxicology screens
- Other bloodwork as indicated
  - Cultures
  - HIV
  - Paraneoplastic panel
  - Autoimmune studies
- Consider head CT, brain MRI, and EEG
Catatonia vs. Delirium

• DSM-5 states that catatonia cannot be diagnosed when symptoms are present exclusively in the setting of delirium
• Clinical practice suggests that most patients with neuromedical etiology for catatonia also have delirium
• 12-37% of patients with delirium may have features of catatonia
  – More commonly associated with hypoactive delirium and more common in women
  – Common features of catatonia include excitement, immobility, mutism, negativism, staring, withdrawal

Oldham 2015, Grover 2014
Subtypes of Catatonia

• DSM-5 specifiers:
  – Hyperactive
  – Hypoactive
  – Mixed level of activity

• Malignant Catatonia (aka Lethal Catatonia)
  – Characterized by severe muscle rigidity, hyperthermia, and autonomic instability
    • Delirious Mania
    • Neuroleptic Malignant Syndrome
    • Serotonin Syndrome

APA 2013, Mann 1986
Management of Catatonia

• Identify the underlying cause.
  – Perform full psychiatric evaluation to identify mood or psychotic disorders.
  – Obtain collateral information about patient’s mood and behavior prior to admission.
  – Perform medical workup, especially for those with other symptoms of medical illness.

• Frequent vital signs
• Supportive care
• Remove possible culprit medications
• Initiate treatment with medications or ECT
Treatment of Catatonia: Benzodiazepines

- Intravenous lorazepam is greatly preferred
  - Quick onset of action
  - Despite a shorter half-life than other benzos, effective clinical activity may be longer because tissue distribution is less rapid and extensive
  - Also demonstrates a higher binding affinity for GABA\(_A\) receptor
- Initial dose of 2mg
  - Follow-up dose based on response and sliding scale of suspicion
- If established efficacy or diagnosis certain, continue with standing regimen
  - 8-24mg/day is typical
  - Taper very slowly after improvement

Denysenko 2015
Treatment of Catatonia: ECT

• Effective in 85-90% of cases; 60% of cases that fail medication

• Should be considered for failure to respond to lorazepam in 48-72 hours, malignant symptoms, excited subtype

• Maintenance ECT often required
Treatment of Catatonia: Alternatives

- NMDA receptor antagonists
  - Amantadine (18 cases)
    - May also have dopamine agonist activity
    - Start at 100mg daily
    - Titrate by 100mg every 3-4 days to maximum of 400mg in 2-3 divided doses
  - Memantine (9 cases)
    - Start at 5mg bid
    - Increase to 10mg bid if ineffective
- Antiepileptic medications
  - Carbamazepine (7 cases)
    - 100-1000mg daily
  - Valproic acid (5 cases)
    - 600-4000mg daily
  - Topiramate (4 cases)
    - 200mg daily

Beach 2015
Treatment of Catatonia: Alternatives

• Antipsychotic medications
  – Hypothesized to work through 5-HT1A agonism and 5-HT2A antagonism, which may lead to increased dopamine in the prefrontal cortex.
  – Aripiprazole (9 cases)
    • 3-30mg daily
  – Clozapine (9 cases)
    • 150-300mg daily
  – Olanzapine (7 cases)
    • 2.5-20mg daily
  – Risperidone (2 cases)
    • 0.5-8mg daily
  – Ziprasidone (2 cases)
    • 40-160mg daily
Treatment Algorithm

Intravenous lorazepam
(initial test dose, then 6-8mg daily)

Electroconvulsive therapy
(at least 6 treatments)

Glutamate (NMDA) antagonist
(amantadine or memantine)

Anti-epileptic medication
(carbamazepine or valproic acid)

Atypical antipsychotic
(aripiprazole, olanzapine, clozapine)
Neuroleptic Malignant Syndrome (NMS)

• No DSM diagnostic criteria
• Expert panel criteria:
  – Exposure to dopamine antagonist (or removal of dopamine agonist) within past 72 hours
  – Hyperthermia
  – Rigidity
  – Mental status alteration
  – CK elevation (>4 times upper limit of normal)
  – Autonomic instability
  – Hypermobility
  – Exclusion of other medical or substance-induced causes

Guerra 2011
NMS: Complications and Treatment

• Complications
  – Rhabdomyolysis
  – Seizures
  – Respiratory failure
  – Acute kidney injury
  – Sepsis
  – Acute MI
  – Acute liver failure
  – Pulmonary embolism

• Mortality rate 5.6%

• Treatment
  – Remove offending agent
  – Similar treatment to catatonia

Modi 2015
Serotonin Syndrome (SS)

• Sometimes considered a subtype of malignant catatonia

• Symptoms:
  – Spontaneous clonus
  – Inducible clonus AND agitation or diaphoresis
  – Ocular clonus AND agitation or diaphoresis
  – Tremor AND hyperreflexia
  – Hypertonia AND hyperthermia AND ocular clonus or inducible clonus

• Classically induced by combination of MAOI with serotonergic medication

• Now more commonly seen with polypharmacy or overdose

• Clues to Serotonin Syndrome
  – Look for it in patients with antidepressant overdose
  – Look for it in any patient on >4 psychiatric medications
  – Consider it in all catatonic patients

Dunkley 2003
Treatment of Serotonin Syndrome

• Supportive treatment and wash-out is usually all that is needed
  – May use benzodiazepines to manage agitation or if catatonic symptoms are present
  – Short-acting antihypertensives

• If this is not working, can consider cyproheptadine (5-HT1A and 5-HT2A antagonist)
References


References


References