Movement disorders for psychiatrists

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Learning objectives: Describe neuroleptic-induced movement disorders
Acute dystonic reaction
Neuroleptic malignant syndrome
Drug-induced parkinsonism
Akathisia
Tardive Dyskinesia
Acute Dystonic reaction

Rapidly developing, severe dystonia occurring after exposure to a dopamine receptor blocking or depleting agent (all typical and atypical antipsychotic agents and tetrabenazine)

Other causative/contributing drugs: cocaine, lithium SSRI's

Acute Dystonic Reaction

Clinical Features:

- Any combination of retrocollis, trismus, tongue protrusion, upward and lateral deviation of eyes
- Back arching, lateral trunk flexion less common
- Most dangerous: Laryngospasm

Time of onset:
- 50% within 1 day of therapy
- 90% within 5 days
Acute Dystonic Reaction

Risk Factors:
- Young age
- Male gender (Male: Female, 2:1)
- High potency neuroleptic
- High dosage of offending drug
- Previous ADR
- Cocaine USE

Acute Torticollis

Rapid onset, over minutes to hours, of severe, often very painful, eccentric position of the head in either the horizontal or vertical plane or both

Acute Torticollis: Etiology

Never idiopathic
- Iatrogenic: after tonsillectomy**
- Infectious: tonsilar/retropharyngeal abcess, pharyngitis (Grisel's syndrome)**
- Localized tetanus
- Traumatic atlantoaxial dislocation

**edema and enhanced flexibility of alar ligaments
Acute Dystonic Reaction

Treatment

Acute:
- Anticholinergics (benztropine) IV > oral
- Antihistamine (diphenhydramine) IV > oral
- 2nd Line: diazepam IV

Chronic:
Continue oral treatment for 1 week, then taper

Caution: rapid withdrawal of anticholinergics can re-exacerbate acute dystonic reaction

Acute Dystonic Reaction

Prevention:
If future dopamine acute treatment is required
- Ask yourself, is it really required?
- Pre-treat with Anticholinergic agents
- Only 7 days of therapy required
Neuroleptic Malignant Syndrome

Clinical Syndrome:
- Fever > 38º C
- Rigidity (chorea, dystonia, myoclonus)
- Alteration in consciousness
- Autonomic instability (BP, arrhythmias)
**Neuroleptic Malignant Syndrome**

**Clinical Syndrome:**
- Fever > 38°C
  - R rigidity (chorea, dystonia, myoclonus)
  - Alteration in consciousness
  - Autonomic instability (BP, arrhythmias)
- Onset usually after initiation or increase in DRBA
  - 16% onset within 1 day
  - 30% within 2 days.
  - 50% within 7 days
  - 100% within 30 days

**Sequence of clinical signs:**
- *Mental status changes*
- Rigidity
- Hyperthermia
- Autonomic dysfunction

Levenson, JL 1985: 340 cases reviewed

**Risk Factors**
- Young age (20 - 50)
- Male gender
- Recent onset or increase in neuroleptic dosage
- Intramuscular administration of drugs
- Presence of other extrapyramidal syndromes
- Agitation
- Dehydration
- Previous NMS or previous CK elevation
Neuroleptic Malignant Syndrome

Drugs Associated with NMS:
- All typical and atypical antipsychotic agents
- Antiemetics (metoclopramide, prochlorperazine)
- Tetrabenazine or Reserpine
- Tricyclic antidepressants?
- SSRI antidepressants?
- Carbamazepine?
- Lithium?

Withdrawal/reduction of dopaminergic medication in Parkinson’s patients—including post DBS (Parkinson hyperpyrexia syndrome (PHS))

NMS: Is it same for typical vs. atypical neuroleptics?

NMS due to atypical agents is likely:
  a) less severe
  b) atypical (one or more features absent)
  c) associated with lower mortality
Parkinson's Hyperpyrexia vs. Neuroleptic Malignant Syndrome?

Parkinson's Hyperpyrexia:
most at risk:
- young PD patients
- PD patients with history of wearing off (rarely occurs during a wearing off episode)
- PD patients with advanced disease
- post-operative patients with enteral feeding

initial symptom:
- often fever rather than change in mental status

Neuroleptic Malignant Syndrome

laboratory aids to diagnosis

↑CK - usually > 2000 IU/L

↑WBC
Neuroleptic Malignant Syndrome

Treatment

Supportive:
- Discontinue offending drug
- Rehydration, alkalization of urine
- Reduce body temperature (not aspirin or NSAIDs)
- Support Respiration if needed
- Close monitoring of blood pressure, heart rhythm

Medical:
- Bromocriptine 2.5 QID → 12.5 QID (apomorphine)
- Dantrolene 1 - 10mg/kg per day, TID schedule
- Amantadine 100 - 200mg BID
- Carbamazepine
- Restart dopaminergic drug(s) in Parkinson’s patient
- ECT

Diagnosis of NMS established

Caused by administration of DRBA
- Discontinue DRBA
- Taper and discontinue anticholinergic agents

Caused by withdrawal of dopaminergic drug(s)
- Reinstate previously withdrawn dopaminergic drug(s)
- Institute mechanical cooling (cooling blanket, fans)
- Taper and discontinue anticholinergic agents
- Treat serious autonomic symptoms (arrhythmias, hypotension, hypertension)
- Provide respiratory support if needed
- Institute medical therapy

Rigidity is not prominent.
- Alteration in consciousness more severe.
- Rigidity is prominent.
- Alteration in consciousness less severe

Dantrolene 1-10mg/kg/day
- Bromocriptine 2.5mg TID, rapidly escalating up to 15mg TID, if needed

Significant Improvement
- Can restart DRBA 2 weeks after resolution of NMS

No improvement
- Add Dantrolene
- Add Amantadine 200-400mg/day
- Add Bromocriptine
- Add Amantadine 200-400mg/day
- Consider ECT

Neuroleptic Malignant Syndrome

Outcome

- Most cases improve in 1-5 days after beginning treatment
- Often, total resolution within 1-2 weeks (longer with depot drugs)
- Mortality (5-20%) associated with:
  - Severe rhabdomyolysis
    - Renal Failure
    - D.I.C.
  - Respiratory and cardiac disturbances
Neuroleptic Malignant Syndrome

Re-challenge with Neuroleptic Drugs
- Wait 2 weeks after full recovery**
- If 1st generation neuroleptic, use lower potency
- Use 2nd gen agent, if possible. Avoid lithium
- Monitor for early signs of NMS
- 15% recurrence when the same agent is used again

** ECT to treat psychosis during this time if needed

Most important consideration in the differential diagnosis of NMS:

*Serotonin syndrome*
- diarrhea, myoclonus, shivering tremor, hyperreflexia, clonus, pupillary dilatation

Serotonin Syndrome

<table>
<thead>
<tr>
<th>Comparison with NMS</th>
<th>SRSN</th>
<th>NMS</th>
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</thead>
<tbody>
<tr>
<td>Mental Status Change</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Fever</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Tachypnea/tachycardia</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>+++</td>
<td>0</td>
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<tr>
<td>Diaphoresis</td>
<td>++</td>
<td>+++</td>
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<tr>
<td>Rigidity/bradikinesia</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td>Stupor</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Tremor</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Shivering</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Hyperreflexia/clonus</td>
<td>+++</td>
<td>0</td>
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<tr>
<td>Elevated CK</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Pupillary dilatation</td>
<td>++</td>
<td>0</td>
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</table>
Drug-Induced Parkinsonism

**Causative Agents**
- first generation antipsychotic drugs
- cinnarizine and flunarizine
- metoclopramide
- tetrabenazine
- second generation (atypical) antipsychotic drugs
  - risperidone
  - quetiapine?
  - Ziprasidone
- less common: lithium, SSRI's, valproic acid, amiodarone, Ca+ channel blockers, cyclosporin, lovastatin

Drug-Induced Parkinsonism

**Differences from Parkinson’s Disease**
- more often symmetric
- slightly lower incidence (50%) of rest tremor (?) Dose related
- 2:1 female predominance
- poor response to levodopa
- high incidence of tardive dyskinesia
Drug-Induced Parkinsonism: Pathogenesis

discontinuance of offending drug

resolution of symptoms  persistence of symptoms
Drug-Induced Parkinsonism:
Pathogenesis

discontinuance of offending drug

resolution of symptoms  persistence of symptoms

reversible receptor unmasked neuronal
blockade ("pure") DIP PD toxicity

continued worsening
stable

late recurrence
continued worsening
stable
On lithium, full DIP
Off lithium 9 months, mild DIP
Off lithium 24 months, no DIP
Healthy control
Parkinson’s patient

Distinguishing DIP from unmasked PD

MIBG scintigraphy
Smell test
**Drug-Induced Parkinsonism**

**Treatment**
- Discontinue offending drug—improvement in 2 - 8 weeks, possibly months—*up to 25%, never*
- In mild cases: amantadine? benztrapine?
- In severe or persistent cases: levodopa (unmasked true Parkinson’s disease)

**Akathisia**

An irresistible urge to move, often associated with stereotyped repetitive actions (foot tapping, hand wringing, walking in place)

**Responsible Drugs**

**Definite:**
- Dopamine receptor blocking agents
- Levodopa/dopamine agonists

**Probable:**
- SSRIs (? Serotonin syndrome)

**Uncertain:**
- Tricyclic antidepressants
- Calcium channel blockers
- Carbamazepine
- Buspirone
Akathisia

Treatment
- Discontinue offending drugs
- Medical therapy:
  - Propranolol
  - Anticholinergics (? With EPS only)
  - Diazepam
  - Clonidine
  - * Clozaril (for levodopa-induced)

Tardive Dyskinesia

- Involuntary, repetitive movements
- Can involve orofacial muscles
- Rapid jerks / writhing movements
- Can be dystonic
- Can have myoclonic jerks
- Rates via an Abnormal involuntary movement scale
Tardive Dyskinesia

- Any drug that acts on D2 dopamine receptors
  - Typical antipsychotics (1950's) –
    - 32% of patients at 5 years
    - 57% at 15 years
    - 68% by 25 years (Glazer 1991)
  - Metoclopramide
  - Atypical antipsychotics – 13.1 %
- Modulated by age, race, 5HT polymorphisms

Tardive Dyskinesia

- Weakest drug for the shortest time
  - Atypical > typical
  - Weak data on other modifying drugs

Tardive Dyskinesia

- Few good treatments
  - Benzodiazepenes: Clonazepam
  - Clonidine
  - Odansetron
  - Botox – for focal TD
  - Tetrabenazine
  - Valbenazine
Tardive Dyskinesia

Davis et al., 2017