Bladder Issues in MS patients
– Evaluation and Treatment

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Disclosure: Medtronic, Allergan, Aquinox, Teva
Outline

- Case presentation
- Normal bladder storage and emptying
- Impact of MS on bladder storage and emptying
- Assessment by urodynamics testing
- Neurogenic urinary incontinence associated with MS
  - Behavioral therapy
  - Oral medications
  - Botox (onabotulinumtoxin-A)
- Urinary retention and incomplete bladder emptying
Case presentation

- 67 y.o. F with relapsing remitting MS referred for bothersome urinary incontinence
- Hourly urinary frequency
- Nocturia 4/night
- Urgency urinary incontinence
- Changes pads 5-6 times/day
- Empties well, never require CIC

- Pelvic floor (kegel) exercises
- Multiple anticholinergics
- β3-agonist (Myrbetrix)
- None worked, all she gets was dry mouth from anticholinergics
Physiology: Normal bladder function

- **Sympathetic (hypogastric)**
- **Somatic (pudendal)**
- **Para (pelvic)**

**Pontine micturition Center (PMC)**

- **T10-L2**

- **S2-4**

- The bladder and urinary sphincter are under neurologic control

- Ascending and descending communication is essential for proper function:
  1. **Store without UI**
  2. **Empty without retention**
  3. **Coordination** (bladder & sphincter work in synch)
Physiology: Normal bladder function

- Pontine micturition center (PMC) in the pons
  - Inhibits involuntary voiding

- Sympathetic (T10-L2)
  - Bladder relaxation
  - Bladder neck contraction

- Sacral (S2-S4)
  - Bladder contraction
  - Sphincter contraction
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Diagram:
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- Sacral (S2-S4)
  - Bladder contraction
  - Sphincter contraction
  - Notice the coordination between the bladder and the urinary sphincter (synergy)
Pathology: Complete Sacral SCI or Pelvic Nerve Injury...

- Areflexic bladder
- **Urinary retention**
- **High PVR (post-void residual)**

**Diagram:**
- T10-L2
- Sympathetic (hypogastric)
- Somatic (pudendal)
- S2-4
- Pontine micturition Center (PMC)
- Para (pelvic)
Pathology: Complete Supra-Sacral SCI...

- Involuntary bladder contractions
- Sacral center lost the inhibition from PMC
- **Urinary incontinence**
- Frequency
- Urgency
- Nocturia
Pathology: Complete SCI, High Thoracic or Cervical Levels

- Sacral center lost the inhibition from PMC
- PMC inhibition of Onuf’s nucleus that controls the urinary sphincter is lost
- When bladder contracts, so does the external sphincter => functional obstruction

*Detrusor external sphincter dyssynergia (DESD)*
Pathology: For MS, it can be unpredictable and variable...

Pontine micturition Center (PMC)

T10-L2

S2-4

Sympathetic (hypogastric)

Para (pelvic)

Somatic (pudendal)
Pathology: For MS, it can be unpredictable and variable...

Fontine micturition Center (PMC)

T10-L2 Sympathetic (hypogastric)

S2-4 Para (pelvic)

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Pontine micturition Center (PMC)

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Sympathetic (hypogastric)

(-)

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Rathology: For MS, it can be unpredictable and variable...

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- T10-L2
- Sympathetic (hypogastric)
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Rathology: For MS, it can be unpredictable and variable...

- **Urinary incontinence** (37-72%)
- **Frequency**
- **Urgency**
- **Nocturia** (31-85%)
- **Urinary retention**
- **High PVR**
- **DESD (functional obstruction)** (2-52%)
- **Combination of above**

Wyndaele et al 2005
Pathology: For MS, it can be unpredictable and variable...

- Urinary symptoms may be the initial complaints in ~15% of MS patients
- **Acute** urinary retention in young otherwise healthy women without any other explanations
- **Acute** onset of urinary frequency, urgency, or urinary incontinence
- In chronic MS pts, UDS patterns can change over time w/ and w/o new Sx

Wyndaele et al 2005
Objective evaluation: Urodynamics (UDS) testing

\[ P_{\text{det}} = P_{\text{ves}} - P_{\text{abd}} \]

- Voided flow
- Vesical
- Abdominal
- Detrusor
- Pelvic floor

EMG
Detrusor Overactivity (DO) on Urodynamics (UDS)

- Detrusor overactivity is most common UDS finding (34-99%)
- *Neurogenic urgency urinary incontinence (UUI)*

Wyndaele et al 2005
Loss of Detrusor Compliance on Urodynamics

- Storage pressure exceeding 40 cm H$_2$O put upper tract at risk
- *Urinary incontinence, Upper tract deterioration*
This is what the sphincter should do during bladder contraction.

Relax (synergy)
Detrusor External Sphincter Dyssynergia (DESD)

• Sphincter dyssynergia 30-60% MS patients (cervical)
• **Functional Obstruction, Urinary Retention, High PVR**
Areflexic or Hypocontractile Bladder on Urodynamics

- About 12-38% of cases
- **Urinary Retention, High PVR, Hydronephrosis, Stones**
What urodynamics parameters put the upper tract at risk?

- 113 MS pts, f/u 4 years GU
- 66 had UDS and Renal US
- 11/66 (16%) abnormal US
- But all are minor caliectasis without clinical significance
- Neither Cr or specific UDS findings predicts US finding
- Major upper tract damage is uncommon in MS pts
What urodynamics parameters put the upper tract at risk?

- 94 MS pts, never seen GU
- Renal US on all pts
- Cr clearance on all pts

- n=3 (3.3%) abnormal Cr
- n=5 (5.4%) abnormal US

- All those who had abnormal Cr or US had progressive MS (instead of relapsing and remitting MS)

- Renal deterioration is rare
What urodynamics parameters put the upper tract at risk?

- But caution in the following types of patients:

1) **DESD** *(detrusor external sphincter dyssynergia)* esp male, sustained and prolonged high pressure bladder contractions.
What urodynamics parameters put the upper tract at risk?

- But caution in the following types of patients:

1) **DESD (detrusor external sphincter dyssynergia)** esp male, sustained and prolonged high pressure bladder contractions.

2) **Loss of detrusor compliance** with storage pressure >40 cm H$_2$O
Urologic Evaluation of MS Patients

- **History**

- **Focused physical examination**
  - Cognitive function (impact anti-cholinergics, behavioral tx, aware of urge?)
  - Bowel function or constipation (impact anti-cholinergics use?)
  - Manual dexterity (ability to do CIC?)
  - Functional limitation (mobility, inability to get out of wheelchair?)
  - Other medications (anti-cholinergic properties?) and fatigue

- **UA**

- **Post-void residual (bladder scanner)**

- **Urodynamics in selected patients**
  - If low PVR, normal Cr, renal US, stable neurologic, no UTI ➔ low yield
Management of Common Urologic Issues

• Neurogenic urgency urinary incontinence (UUI)

• Urinary retention, incomplete emptying
Different types of Urinary Incontinence

- **Stress Urinary Incontinence (SUI)**
  - Coughing, sneezing, exercising, standing up

- **Overflow Incontinence**
  - From incomplete bladder emptying, check the PVR
  - Insensate and continuous incontinence

- **Poor Detrusor Compliance**
  - From high bladder storage pressure, needs UDS to diagnose
  - Insensate and continuous incontinence

- **Urgency Urinary Incontinence (UUI)**
  - Urgency ("I got to go"), frequency, nocturia
  - Can be insensate in MS (don’t feel the urge)
Management of Urgency Urinary Incontinence (UUI)

- Clinicians should offer behavioral therapies as initial therapy to patients with UUI:
  - Kegel exercises
  - Distraction strategies
  - Bladder drill (extends time between voiding, timed voiding)
  - Fluid management (6 cups of 8 oz fluid; ~1.5L/day)
  - Avoidance of bladder “irritants”
    - Caffeine (coffee, tea), Soda (carbonated drinks), Acidic (lemonade, citrus, OJ, grapefruit juices), Spicy food
  - Manage the constipation
  - Weight loss
  - Stop smoking
Management of Urgency Urinary Incontinence (UUI)

• Clinicians should offer **oral anti-muscarinics**, or **oral β3-adrenoceptor agonists** (mirabegron).

• If an immediate release (IR) and an extended release (ER) formulation are available, then **ER formulations should preferentially** be prescribed because of lower rates of dry mouth (e.g., Rx ditropan XL instead of ditropan TID).

• If a patient experiences **inadequate symptom control** and/or **unacceptable adverse** drug events with one anti-muscarinic medication, then a dose modification or a different anti-muscarinic medication or a β3-adrenoceptor agonist may be tried.
Management of Urgency Urinary Incontinence (UUI)

- Clinicians should not use anti-muscarinics in patients with narrow angle glaucoma unless approved by the treating ophthalmologist and should use anti-muscarinics with extreme caution in patients with impaired gastric emptying or a history of urinary retention (high PVR).

- Clinicians should manage constipation and dry mouth before abandoning effective anti-muscarinic therapy. Management may include bowel management, fluid management, dose modification or alternative medications.

- β3-adrenoceptor agonist (mirabegron) does not have dry mouth or anti-cholinergic adverse effects.
Management of Urgency Urinary Incontinence (UUI)

- Clinicians must use caution in prescribing anti-muscarinics in patients who are using other medications with anti-cholinergic properties.

- Clinicians should use caution in prescribing anti-muscarinics or β3-adrenoceptor agonists in the frail patients or those with cognitive impairment.

- Intravesical anti-cholinergics (e.g. ditropan) may be an option in patients who is already doing CIC.
Table 1: Pharmacological characteristics of commonly used anti-muscarinic drugs for OAB

<table>
<thead>
<tr>
<th>Antimuscarinic (amine)</th>
<th>Chemical Structure (kDa)</th>
<th>Molecular Weight (kDa)</th>
<th>Lipophilic</th>
<th>pKi for M1 receptor</th>
<th>pKi for M3 receptor</th>
<th>T1/2 (hr)</th>
<th>Food Bioavailability</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin (Desethyl-oxybutynin)</td>
<td>tertiary</td>
<td>357.5</td>
<td>High</td>
<td>9.9</td>
<td>12.3</td>
<td>3-Feb</td>
<td>25% Increase when taken with food</td>
<td>Dry mouth (71.4%), dizziness (16.6%), constipation (15.1%), somnolence (14%), nausea (11.6%), urinary hesitancy (9.5%), urinary retention (6%)</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>tertiary</td>
<td>426.6</td>
<td>Moderate</td>
<td>8.2</td>
<td>9.1</td>
<td>13-19</td>
<td>None</td>
<td>Dry mouth (35%), constipation (21%), dyspepsia (9%), UTI (5%), abdominal pain (4%)</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>tertiary</td>
<td>362.5</td>
<td>Low-moderate</td>
<td>7.6</td>
<td>8</td>
<td>45-68</td>
<td>3% increase</td>
<td>Dry mouth (28%), constipation (13%), UTI (5%), blurry vision (5%)</td>
</tr>
<tr>
<td>Tolterodine*</td>
<td>tertiary</td>
<td>325.5</td>
<td>Low-moderate</td>
<td>8.5</td>
<td>7.9</td>
<td>3</td>
<td>53% increase</td>
<td>Dry mouth (39.5%), dysuria (1-10%), blurred vision (5%), urinary retention (1.7%)</td>
</tr>
<tr>
<td>Fesoterodine*</td>
<td>tertiary</td>
<td>411.6</td>
<td>Low-moderate</td>
<td>6.2</td>
<td>&lt;6.0</td>
<td>5</td>
<td>None</td>
<td>4 and 8 mg: Dry Mouth (18.8-34.6%), constipation (4.2-6.0%), nausea (0.7-1.9%), UTI (3.2-4.2%), dry eyes (1.4-3.7%), urinary retention (1.1-1.4%), peripheral edema (0.7-1.2%), Insomnia (1.3-0.4%)</td>
</tr>
<tr>
<td>5-HMT hydroxymethyl tolterodine*</td>
<td>tertiary</td>
<td>341.49</td>
<td>Low-moderate</td>
<td>8.7</td>
<td>8.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tropium</td>
<td>quaternary</td>
<td>392.1</td>
<td>Very low</td>
<td>9.1</td>
<td>9.3</td>
<td>20</td>
<td>80% decrease in AUC</td>
<td>Dry mouth (20%), constipation (10%), headache (4%)</td>
</tr>
</tbody>
</table>

Practically no major differences between the different anti-cholinergics (meta-analysis)
Management of Urgency Urinary Incontinence (UUI)

- The majority of pts prescribed anti-cholinergics don’t stay on it

Chancellor et al 2013
Management of Urgency Urinary Incontinence (UUI)

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Chancellor et al 2013
Management of Urgency Urinary Incontinence (UUI)

- Clinicians may offer intradetrusor onabotulinumtoxinA (Botox) as treatment in the patient who has been refractory to treatments.
- FDA approved for both idiopathic and neurogenic UUI (OAB, MS, SCI, CVA)
- Office procedure (local)
- Last about 9-10.5 months
Management of Urgency Urinary Incontinence (UUI)

- International phase 3 RCT (63 clinical centers), 154 MS pts and 121 SCI pts, randomized to placebo, 200 U & 300 U Botox

Cruz et al, Eur Urol 2011
Management of Urgency Urinary Incontinence (UUI)

- International phase 3 RCT (63 clinical centers), 154 MS pts and 121 SCI pts, randomized to placebo, 200 U & 300 U Botox

*Cruz et al, Eur Urol 2011*
Management of Urgency Urinary Incontinence (UUI)

- No advantage of 300 U over 200 U Botox
- Risks: UTI and urinary retention

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 90)</th>
<th>OnabotA 200 U (n = 91)</th>
<th>OnabotA 300 U (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>During the first 12 wk, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All AEs</td>
<td>50 (55.6)</td>
<td>63 (69.2)</td>
<td>68 (76.4)</td>
</tr>
<tr>
<td>AEs with incidence ≥5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UTI</td>
<td>20 (22.2)</td>
<td>25 (27.5)</td>
<td>34 (38.2)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>3 (3.3)</td>
<td>18 (19.8)†</td>
<td>28 (31.5)†</td>
</tr>
<tr>
<td>Haematuria</td>
<td>3 (3.3)</td>
<td>5 (5.5)</td>
<td>7 (7.9)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>2 (2.2)</td>
<td>2 (2.2)</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (2.2)</td>
<td>1 (1.1)</td>
<td>5 (5.6)</td>
</tr>
</tbody>
</table>

- For patients already doing CIC, start with 200 U (recommended FDA dosing for **neurogenic** UUI)
- For patients not doing CIC, start with 100 U, and monitor PVR
Management of Urgency Urinary Incontinence (UUI)

- 100 U Botox is the recommended dosing for **non-neurogenic** UUI (overactive bladder)
- Multi-center double-blind RCT, 144 MS pts randomized to placebo vs. 100 U Botox.

Good efficacy.

**Lower and more acceptable retention risk:**

- Placebo = 2.6%
- 100 U Botox = 15%

Denys et al, 2016; Bruckner 2017
Management of Urgency Urinary Incontinence (UUI)

- How about long term repeated Botox use?
- 4-year open label study, 231 MS & 157 SCI

Kennelly et al, 2017
Management of Urgency Urinary Incontinence (UUI)

- Clinicians may consider **sacral neuromodulation** (**InterStim**) in those who fail other treatments like Botox
- Not FDA-approved for neurogenic bladder
- Limited data on efficacy
  - Meta-analysis: 84% pass test, 92% remains successful at 26M f/u
- MRI contraindication (can only do head MRI, but not spine)
Management of Urinary Retention or elevated PVR

• There is no universally accepted PVR that defines urinary retention in the MS population (non-neurogenic ≥300 mL)

• CIC (clean intermittent catheterization)
  ➢ Hydrophilic catheter decreased UTI & urethral trauma (systematic review)
  ➢ CIC improved QOL in 52%, decreased QOL in 25%, unchanged in 19%

• Crede or valsalva? (consider if no DESD and “lower PVR”)
• Leave it alone and follow up? (asymptomatic, normal US, Cr)

• If indwelling catheter, use suprapubic tube
  ➢ Less bacteriuria and less pain compared to foley (Cochrane review)

Stoffel 2017; Shermout 2017; James 2014; Kidd 2015
Case presentation

- 67 y.o. F with relapsing remitting MS with urinary urge incontinence (UUI), frequency & nocturia
- OnabotulinumtoxinA 100 units
- Done in office under local
- Two weeks later:
  - Improved remarkably
  - Voided 4-5 times/day (instead of hourly)
  - Nocturia X1 (instead of 4/night)
  - One thin liner a day (instead of 5-6 pads/day)
  - Botox lasted about 9 months
  - Had another bladder Botox
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