Lithium Related Nephrogenic Diabetes Insipidus: A Case Study

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Objectives
- Identify the prevalence and impact of lithium induced nephrogenic DI
- Review diagnostic criteria and differential diagnosis of nephrogenic DI
- Describe strategies to reduce the risk of nephrogenic DI
- Discuss treatment strategies and management of lithium-induced nephrogenic DI

Renal Excretion of Lithium
- Lithium is cleared by the kidney
- 20% excreted in the urine
- Reabsorption in the proximal tubule
  - Follows Sodium reabsorption
- Factors that increase sodium reabsorption also increase Li levels
  - Volume depletion, low salt intake, ischemia, CHF, Cirrhosis, Diuretics, NSAIDs and ACE-Is

Renal Handling of Lithium

QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.
Renal Toxicity of Chronic Li Therapy

- Nephrogenic Diabetes Insipidus
- Renal Tubular Acidosis
- Nephrotic Syndrome
- Chronic Tubulointerstitial Disease

Chronic Tubulointerstitial Disease

- Focal interstitial nephropathy
  - Interstitial Fibrosis
  - Tubular Atrophy
  - Distal tubular dilatation and microcyst formation
    - Results from proliferation of distal tubular cells
  - Glomerulosclerosis

A: Image of histological section showing interstitial fibrosis, tubular atrophy, and interstitial fibrosis.
Nephrogenic DI

- 15-40% of all pts treated with Li develop polyuria
- 12% have clinically established NDI
- Evidence for renal defect:
  - Increased plasma ADH levels
  - Unresponsiveness to exogenous dDAVP
  - Impaired cAMP generation by collecting tubules exposed to Li

Boton R et al., AJKD 1987
Case Study

- 45 yr old AAM with DMII, HTN, obesity, MDD transferred to your clinic
- Lithium augmentation therapy x 6 months
- Chief Complaint: “I can’t stop peeing”
- Questions???

Case Study (Review of Systems)

- Polyuria secondary or primary issue to the polydipsia?
- Frequency vs Polyuria?
  - Urological Studies
- Solute Diuresis vs Water Diuresis?
  - Glycemic Control
  - Sodium (and protein) intake
Major Causes of Polyuria

<table>
<thead>
<tr>
<th>Water Diuresis</th>
<th>Solute Diuresis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Appropriate</strong></td>
<td><strong>Inappropriate</strong></td>
</tr>
<tr>
<td>Primary Polydipsia</td>
<td>Central DI</td>
</tr>
<tr>
<td>Dilute IVF</td>
<td>Nephrogenic DI</td>
</tr>
<tr>
<td>Saline IVF</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Postobstructive diuresis</td>
<td>Protein Feeds</td>
</tr>
<tr>
<td></td>
<td>Na wasting nephropathy (rare)</td>
</tr>
</tbody>
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Diagnostic Algorithm

Case Study (General Diagnostic Evaluation)

- Basic Metabolic Panel
  - Hypercalcemia, Hypokalemia related NDI
- Spot Urine Na, Urine Osm
  - First AM void preferable
- Additional Studies:
  - Urological Evaluation (eg, Urodynamic Studies, cystoscopy)
  - Glycemic Studies (eg, HbA1c)
  - 24 hour urine Na and osmolality collection
Diagnostics (Chronic Lithium therapy)

- **Initial Panel:**
  - Complete Metabolic Panel, UA, protein/creatinine ratio, ?TSH, ?PTH, ?24 hour CCl

- **Additional studies for maintenance Li therapy:**
  - BMP, Li trough

- **As indicated:**
  - AM Urine Osm, Urine Na (first void)
  - 24 hour CCl
  - Thyroid studies
  - PTH

Treatment Options for Li Induced NDI

- Cessation/Minimization of Li
  - Some cases are irreversible

- Amiloride
  - Blockade of ENaC

- Hydrochlorothiazide PLUS low-Sodium diet
  - Volume contraction → ↑ proximal fluid reabsorption → ↓ distal delivery → ↓ UOP

- Indomethicin plus dDAVP
  - Indomethicin inhibits PGE
  - PGE inhibitors ADH in the collecting tubule

Therapeutic Effects

- **Urine Osmolality = Total Dietary Osm/ Total Urinary Volume**

- **Diuretic Therapy**
  - 2x increase in Uosm = 50% decrease in Urinary Volume

- **Dietary Changes**
  - 25% decrease in Dietary Osmolar load (primarily sodium) = 25% decrease in Urinary Volume
Amiloride Therapy

- Nine patients with thirst, excessive urinary frequency and U/Vol > 3L/24 hrs
- Amiloride 5mg BID x 2 wks, then 10mg BID for total of 6 months
- Effects were sustained for 6 months of observation

Batlle DC et al., NEJM 1985

Case Study (cont)

- Sodium discretion
- Amiloride 5 mg qd

- 3 months later... pt is admitted to ED with diffuse abdominal pain
  - CT imaging suggests infarcted bowel

- Taken to OR and has emergent partial colectomy
  - Insulin/parental/abx gtts and NS 83cc/hr
Case Study (cont)

- 48 hour post op:
  - Na 152, K 3.5, Cl 120, CO2 20, BUN 66, SCr 1.5, Anion gap 12, Serum glucose 125
  - 4.5 liters UOP in past 24 hours (negative fluid balance)
  - Urine Sodium 40, Urine Crt 75, Urine Osm 450, Serum Osm 337

- Is there a water diuresis?
  - Calculate Electrolyte Free Water clearance (EFCW)
    - Urine K (10)

Case Study (cont)

- Electrolyte-free water clearance
  - Urine flow rate x (1 - (Urine [Na+K]/Serum Na))
    - 4500cc x (1 - (40+10)/152))
    - 4500cc x (1 - 50/152))
    - 4500cc x (1 - 0.33)
    - 4500cc x 0.67

  - 3015 cc free water clearance (positive clearance)
    - Negative free water balance

Summary

- Metabolic studies and careful ROS necessary for correct diagnosis of Li NDI

- Treatment options are available
  - Solute restriction/Diuretic therapy cornerstone of treatment
  - Early intervention will have most benefit in short and long term management of Li NDI
Questions??