Clinical Aspects of Hyponatremia & Hypernatremia
Case Presentation: History

62 y/o male is admitted to the hospital with a 3 month history of excessive urination (polyuria) and excess water intake up to a gallon per day. His wife noted that he had lost weight, became forgetful and irascible.
Case Presentation: Physical Examination

Emaciated, somnolent 62 y/o man in no acute distress. Multiple signs of dehydration were evident including low blood pressure upon standing (orthostatic hypotension), loss of normal skin resilience, sunken eyeballs, and low intravascular volume. In addition he was confused, disoriented and had reduced level of consciousness.
Case Presentation: Laboratory I

Blood Tests:
Sodium 150 mEq/L (Nl 138-142)
Chloride 106 mEq/L (nl 95-100)
Kidney Function Decreased 50%
Calcium 16.5 mg/dl (Nl 8-10)

Urine Tests:
Specific gravity 1.008 (Nl for dehydration 1.025-1.035),
Urine sodium Na 15 mEq/L (low), Osm 280 mOsm (low for dehydration)
Case Presentation: Laboratory II

- Serum protein electrophoresis: Abnormal amount of pure (monoclonal) immunoglobulin
- Bone Marrow Biopsy: Multiple Myeloma- a malignant tumor of plasma (immune system) cells that causes
  – Monoclonal immunoglobulin excess
  – high blood calcium by break down of the skeleton.
Signs of Polyuria due to Renal Concentrating Defect

- Orthostatic Hypotension
- Low urine osmolality
- Hypernatremia
  - Excess free water loss
  - Insufficient free water intake
Polyuria: Differential Diagnosis

- **Volume Depletion**
  - Diabetes Insipidus
    - Central
    - Nephrogenic
  - Diuretics
    - Osmotic
    - Drugs

- **Normal Volume**
  - Primary Polydipsia
Systemic Consequences of Chronic Hypercalcemia
(High Blood Calcium Concentration)

- Neuro: Altered Mental Status, Muscle Weakness
- GI: Anorexia, nausea and vomiting
- Renal Concentrating Defect
  - Polyuria, polydipsia
  - Hypernatremia (coupled with decreased intake of water from loss of appetite and altered mental status)
Consequences of Hypercalcemia: Renal, Fluid and Electrolyte

- **Volume Depletion**
  - Decreased intake due to anorexia, nausea and vomiting
  - Nephrogenic diabetes insipidus (NDI) causing free water loss
- **Hypernatremia from Nephrogenic Diabetes Insipidus**
- **Renal Insufficiency**
  - Decreased blood flow to kidney
  - Calcification of the kidney itself
Diabetes Insipidus (DI)

- Excessive water loss by the kidney
- Inability of kidney to concentrate the urine
  - Deficiency of Antidiuretic Hormone (ADH)—Central DI
  - Renal resistance to ADH

Central DI – Lack of ADH

Nephrogenic DI – Resistance to ADH
Nephrogenic Diabetes Insipidus: Common Causes

- Many chronic renal diseases
- Electrolyte disorders
  - High Blood Calcium Hypercalcemia
  - Low Blood Potassium Hypokalemia
- Drugs
  - including Lithium, AMP-B, Demeclocycline, Gentamicin, cisplatin, others
- Dietary abnormalities, e.g. decreased NaCl or protein intake
Hyper (High) natremia and Hypo (Low) natremia: Water deficiency and water excess

- Water Excess: Na 130
- Normal Water: Na 140
- Water Deficiency: Na 150
Pathogenetic Mechanisms of Hypernatremia

<table>
<thead>
<tr>
<th>Condition</th>
<th>Serum Sodium</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure Water Loss</td>
<td>$\frac{\text{Na}}{\downarrow \text{TBW}}$</td>
<td>Diabetes Insipidus</td>
</tr>
<tr>
<td>Sodium and Water Loss</td>
<td>$\downarrow \frac{\text{Na}}{\downarrow \downarrow \text{TBW}}$</td>
<td>Osmotic Diuresis</td>
</tr>
<tr>
<td>Sodium Gain</td>
<td>$\uparrow \frac{\text{Na}}{\text{TBW}}$</td>
<td>Hypertonic NaHCO$_3$</td>
</tr>
</tbody>
</table>
Central Diabetes Insipidus

Normal Person
Water restricted

Patient with Central DI
Water Restricted

High AVP

Zero AVP

Urine Flow Low
Uosm 1000

Urine Flow High
Uosm 200
Nephrogenic Diabetes Insipidus

Normal Person
Water restricted

Patient with Nephrogenic DI
Water Restricted

Urine Flow Low
Uosm 1000

Urine Flow High
Uosm 250

High AVP

Cortex

Medulla

H₂O

H₂O

H₂O

H₂O
Hypercalcemia as a Cause of Nephrogenic Diabetes Insipidus

- Any chronic hypercalemic state
- Common cause of NDI in Adults
- Mild hypernatremia (145-150) typical
- Decreased renal function common
- Reversible with correction of hypercalcemia (unless severe nephrocalcinosis)
Hypercalcemia and Nephrogenic Diabetes Insipidus

- Hypercalcemia Causes Polyuria
- Vasopressin Resistant Concentrating Defect
- Direct Effect of Calcium on Renal Water Handling
- Independent of GFR, PTH, Vitamin D, Calcitonin
How does Hypercalcemia cause Nephrogenic Diabetes Insipidus?

- Decreased delivery of solute to the loop of Henle (reduced GFR)
- Inhibition of NaCl transport in the thick ascending limb
- Inhibition of vasopressin-mediated water permeability in the terminal collecting duct
Hypercalcemia and Nephrogenic Diabetes Insipidus

- Direct Effect of Calcium on Renal water Handling
- Vasopressin-Resistant
- Independent of GFR, PTH, Vitamin D and Calcitonin
Osmotic Diuresis

Normal Person
Water restricted

Normal person Mannitol Infusion
Water Restricted

Urine Flow Low
Uosm 1200

Urine Flow High
Uosm 400
Osmotic Diuresis

Poorly reabsorbed Osmolyte

H$_2$O  H$_2$O  H$_2$O

H$_2$O  H$_2$O  H$_2$O

Na  Na  Na

H$_2$O  H$_2$O  H$_2$O

Na  Na  Na

Osmolyte = glucose, mannitol, urea

Hypotonic Saline
Effect of Osmotic Diuresis on Uosm

- Normal
- Partial Central DI
- Complete Central DI
How to determine the cause of polyuric states: Water Deprivation and ADH responsiveness

• Step 1: Water deprivation
• Step 2: Measure Urine Osmolality
• Step 3: Administer exogenous dose of ADH
• Step 4: Repeat Urine Osmolality Measurement to evaluate response to ADH
## Differentiating Polyuric States: Dehydration and AVP Stimulation Tests

<table>
<thead>
<tr>
<th>Condition</th>
<th>Uosm Max dehydration</th>
<th>Uosm Max after AVP</th>
<th>% Change</th>
<th>Uosm Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1068 ± 69</td>
<td>979 ± 79</td>
<td>-9 ± 3</td>
<td>&lt; 9%</td>
</tr>
<tr>
<td>Psychogenic Polydipsia</td>
<td>738 ± 53</td>
<td>780 ± 73</td>
<td>5 ± 2</td>
<td>&lt; 9%</td>
</tr>
<tr>
<td>Partial Central DI</td>
<td>438 ± 34</td>
<td>549 ± 28</td>
<td>28 ± 5</td>
<td>&gt; 9% &lt; 50%</td>
</tr>
<tr>
<td>Complete Central DI</td>
<td>168 ± 13</td>
<td>445 ± 52</td>
<td>183 ± 41</td>
<td>&gt; 50%</td>
</tr>
<tr>
<td>Nephrogenic DI</td>
<td>124</td>
<td>174</td>
<td>42</td>
<td>&lt; 50%</td>
</tr>
</tbody>
</table>

Calculating Water Deficit in Hypernatremia Due to Pure Water Loss

- Serum Na 150, Normal Na 140, 70 kg man
- Total Body Water Deficit =

\[
\text{BW in kg} \times 0.6 \times \frac{150 - 140}{140}
\]

\[
70 \times 0.6 \times [0.06] = 2.8 \text{ L}
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